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UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

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| JACOB GUNVALSON, CHERI AND JOHN GUNVALSON, AS GUARDIANS FOR JACOB GUNVALSON, AND CHERI AND JOHN GUNVALSON, INDIVIDUALLY,<br><br>Plaintiffs,<br><br>v.<br><br>PTC THERAPEUTICS, INC.,<br><br>Defendant. | Civil Action No. 08-3559 (WJM) (MF)<br><br>**DECLARATION OF MIKE HATCH**<br><br>***DOCUMENT FILED ELECTRONICALLY*** |

MIKE HATCH, of full age, declares as follows:

1. Along with co-counsel at Saiber LLC, I represent Plaintiffs Jacob, Cheri and John Gunvalson in the above-captioned matter.

2. A true and correct copy of an article from FDA Consumer Magazine, dated January 2000, entitled "*Experimental Treatments? Unapproved But Not Always Unavailable*" is attached hereto as Exhibit 1.

3. A true and correct copy of a January 2004 Guidance Document issued by the U.S. Food and Drug Administration is attached hereto as Exhibit 2. The Guidance Document, published in the *Federal Register*, offers guidance to the pharmaceutical industry on how drugs which are yet to be approved may be provided to a patient under "compassionate use" exceptions such as a protocol exception/exemption, a single patient IND, or an expanded access protocol.

4. A true and correct copy of a proposed rule in 21 C.F.R. Part 312, published in the Federal Register on December 14, 2006, is attached hereto as Exhibit 3. Final rulemaking for the proposed rule, which would clarify and add new types of expanded access to investigational drugs for treatment of life threatening disease, is due in Fall 2008.

5. A true and correct copy of a profile of PTC Therapeutics in *Business Week*, dated May 4, 2008, is attached hereto as Exhibit 4.

6. A true and correct copy of a profile of Claudia Hirawat, Senior Vice President of Corporate Development for PTC Therapeutics, Inc. ("PTC Therapeutics" or "PTC"), on PTC's website is attached hereto as Exhibit 5.

7. A true and correct copy of the "Management's Discussion and Analysis" portion of the Securities Registration Statement filed by PTC Therapeutics with the Securities and Exchange Commission in 2006 is attached hereto as Exhibit 6. This document states that the company has not generated any product sale revenues, and that the total revenue loss by PTC since its inception is $92 million.

8. A true and correct copy of various pages of FedSpending.org, which tracks the federal government funding of PTC Therapeutics, is attached hereto as Exhibit 7. These pages indicate that PTC received $8,321,548 in federal funding, involving 20 separate transactions, from 2001 to 2006.

9. I have reviewed the federal government website www.clinicaltrials.gov. I cannot locate any data on the site that reflects that PTC has submitted to the government its expanded use protocols for clinical trials involving PTC124.

10. A true and correct copy of the tabular view entry for the Phase IIb study for PTC124 on the federal government website www.clinicaltrials.gov is attached hereto as Exhibit 8.

I certify that the foregoing statements made by me are true. I am aware that if any of the foregoing statements made by me are willfully false, I am subject to punishment.

MIKE HATCH

Dated: July 15, 2008

# EXHIBIT 1

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FDA Consumer magazine
January-February 2000

U.S. Food and Drug Administration

# Experimental Treatments? Unapproved but Not Always Unavailable

*by Larry Thompson*

The scalpel has failed. The IV tubing stands abandoned on the side of the room. Friends and nurses visit less often. The doctors say the limits of medical knowledge have been reached and there is nothing left for you to do but go home and put your affairs in order.

This is a crushing moment. It's even more frightening than the day the doctors announced that you had a serious and life-threatening disease, such as AIDS, cancer or Alzheimer's disease. For many people, however, the limitations of medical knowledge do not define the limits of human hope. As long as life lingers, many patients will fight on, refusing to give up even when biology is against them. So, they set out on a search for treatment options.

And many alternatives exist. In today's medical bazaar, options range from alternative and complementary therapies like acupuncture and homeopathic and naturopathic medicine to nutritional supplements and macrobiotic diets, home-brewed remedies, and even outright frauds like laetrile. But greater promise resides in the drug development pipeline where tomorrow's therapeutics await proof that they work. Unlike alternative therapies, billions of dollars and decades of scientific study often have been invested in the research that leads to promising new therapies. Might there be, somewhere in that high-priced gauntlet, just the right molecule that cures a patient who is running out of time?

The answer is possibly, but finding it isn't easy. Short of randomly hearing about a promising study through the media, most people know relatively little about what drugs are in development. Even if experimental drugs existed in a database, "it is hard to know which drugs are truly promising," says David Banks of the Food and Drug Administration's Office of Special Health Issues. But on average, about 80 percent of the drugs in testing will ultimately be approved.

Getting your hands on a novel medicine can be even more difficult. Usually, only the company has any supply of the new medicine, which is extremely limited to begin with, and most of what is made will be used in clinical studies.

As if these hurdles are not enough, there is the long-held, but incorrect, public perception that FDA erects regulatory barriers that block patients from getting investigational new drugs (INDs). These are drugs that pharmaceutical companies have in clinical trials to demonstrate their safety and effectiveness, but which have yet to be approved by FDA for marketing. For those with a serious illness, the agency rarely blocks access to unproven medications. But FDA does strive to protect all patients, even those who may be dying, from undue risks associated with investigational new drugs. At the same time, FDA believes that the best way to benefit all patients is to speed promising new therapies through the development and approval process so safety, effectiveness and proper use can be established.

"FDA has worked diligently to balance two compelling, and sometimes competing, factors," says FDA Commissioner Jane E. Henney, M.D. "On one hand, there is the need for the disciplined, systematic, scientifically controlled studies necessary to identify treatments that may improve patient health and that lead to the approval of new drugs. At the same time, there is the desire of seriously ill persons, with no effective options available, to have the earliest access to unapproved products that could be the best therapy for them."

Over the last decade, FDA's institutional philosophy has evolved to be more supportive of thoughtful risk-taking by patients who have run out of options. As a result, the agency has put in place a number of regulatory mechanisms and worked with manufacturers to ensure that seriously ill patients can get access to promising, but not fully evaluated, products. At the same time, FDA has protected the critical scientific studies that must be carried out so that patients, physicians and the agency can determine which drugs are truly safe and effective, and how they can best be used.

"We believe that the best means of providing access to useful medical treatments for all Americans is to continue to shorten the review times," Henney says, "and to continue to work with the industry to shorten development times for drugs, biologics and medical devices."

**The Intervention of AIDS**

Before the 1980s, a more paternalistic medical community argued that it was the government's job to protect patients from possible harm by withholding experimental drugs until there is proof that they work and are safe.

AIDS helped alter that view. Not only did that lethal disease spread with terrifying speed, but it struck a patient population capable of mounting a political response that grabbed the nation's attention and galvanized public health policymakers to reconsider long-held beliefs.

Experimental treatments should be available, The Washington Post quoted one activist at the time, "so people would be able to choose for themselves, working with their doctors, whether they want to risk taking a drug because of the possible benefits."

Critics accused FDA of denying dying patients access to possibly lifesaving drugs. To drive home the point, in October 1988, more than 1,000 gay activists staged a protest outside FDA's Rockville, Md., headquarters, trapping the agency's staff inside.

"FDA is the nexus between the government, the private sector and the consumer," the spokeswoman for one of the protest organizers told the Post. "That's why we're targeting [the agency]."

The protest had an effect. The agency, already focused on the issue by the urgency of AIDS, accelerated its reexamination of the way people with serious and life-threatening diseases could gain access to unproven remedies. Although the treatment IND regulations were finalized in 1987, FDA put in place additional mechanisms to make experimental drugs available to seriously ill patients earlier in the drug development process.

With the activism around AIDS and the demands of people with other serious illnesses for access to unproven treatments, the medical community, including FDA, began to appreciate that the traditional risk/benefit models may have been inappropriate for people with serious and life-threatening diseases. Dying patients were willing to take bigger risks for even the slenderest hope of benefit.

"The hope part of it is that it might work and keep them alive a little longer," says Theresa Toigo, associate commissioner for the Office of Special Health Issues. "Even if it is only two months, by then there might be a cure. It is a wonderful survival instinct."

**Getting Access**

For patients in search of a cutting edge treatment, the possibilities have improved dramatically. First of all, there are more clinical studies under way than ever before. FDA has on file more than 13,000 active drug and biologic studies. These range from a few dozen patients to as many as 50,000 participating in a single investigational new drug trial. More than 100,000 patients are enrolled each year in National Institutes of Health-sponsored studies conducted all over the United States.

Studies with investigational new drugs can be conducted by the federal government, primarily through the National Institutes of Health; by research universities, usually with federal funding, though also through private foundations or drug companies; and by private, for-profit companies on behalf of pharmaceutical manufacturers.

Clinical trials are essential to the development and approval of new drugs. In these studies, a group of human volunteers receiving the investigational therapy are compared with another group that receives either the standard treatment or a placebo. Placebos, sometimes called sugar pills, are any fake treatment that has no therapeutic benefit. This allows the researchers to compare the effect of the treatment to no treatment in otherwise similar patients. When the control group is given the standard treatment, researchers are able to determine whether the experimental treatment provides a better outcome than what is already available.

The clinical trial setting helps ensure that risks are minimized because the research protocol, the set of rules by which the clinical trial is conducted, have been scrutinized by FDA and a local ethics committee called an institutional review board.

"We want to encourage people to participate in the clinical trial process because that is where information is best developed about the drug product," says David Lepay, M.D., director of the division of scientific investigation in FDA's Center for Drug Evaluation and Research.

The downside of being in a clinical trial, indeed the downside of using any unproved medication, is that the new drug may not work. It may even be dangerous and, sometimes, deadly.

Not everyone who wants to participate in a clinical trial can do so. Limits on the number of participants and specific eligibility criteria keep some people out. In addition, it is often inconvenient for the patient to travel to the research center.

When individuals are unable to participate in a clinical study, FDA provides alternative mechanisms for patients and their doctors to get their hands on a promising new drug.

**Beyond Clinical Trials**

In 1987, FDA created a regulatory mechanism (first proposed in 1982) to permit expanded access to investigational drugs outside of controlled clinical trials. The "treatment IND" allows people with serious and life-threatening illnesses to take investigational drugs while the products are being tested in a clinical trial. Typically, however, drugs allowed under treatment INDs already have shown promise and proven safety. In addition to the benefit to individual patients, treatment INDs generate useful

information about how the drug affects larger segments of the patient population than might otherwise receive it in a clinical study.

For example, the AIDS drug Videx (ddI) was made available to people with AIDS outside the clinical trial at a time when the choices for AIDS therapy were few and many people had already exhausted the then available options. Although patients seeking treatment with ddI were told that it was still under study and that there were risks, more than 20,000 decided to take ddI anyway. This not only gave them a better chance to survive but also gave researchers more information about the drug's safety than would have been possible from the some 4,000 patients involved in the clinical studies.

Since the final treatment IND rule was published more than a decade ago, FDA has made more than 40 drug or biologic investigational products available to patients early and has approved 36. Of these, nearly a dozen were for cancer and another dozen for AIDS or AIDS-related conditions.

**Single-Patient INDs**

As with a clinical trial, there may not be an appropriate treatment IND for an individual patient's condition, but there may be a new drug still working its way through development. If enough is known about the drug's safety, and there is some clinical evidence of effectiveness, FDA may allow a patient to become his or her own study. This so-called single-patient IND, or compassionate use IND, virtually ensures that any patient can get access to any investigational new drug.

Although FDA's requirements for a single-patient IND are relatively simple, setting up this kind of access for an individual patient is not. First of all, the company must be willing to provide the new drug to the patient. This can be expensive and time consuming for the company since, in addition to providing the drug, the company needs to track shipments of the drug, create special instructions for its use, and create a way of collecting safety data and a mechanism for tracking outcomes for each patient. Second, the patient must give informed consent, understanding that the drug is not approved and may cause side effects from mild to fatal. Third, the patient's physician must be willing to take responsibility for treating the patient and agree to collect information about the effects of the drug.

Companies sometimes say that they cannot make the drug available to a patient because FDA won't allow it, but that is rarely true. FDA only denies access when there is evidence that the risk of using the experimental drug clearly outweighs any potential benefit to the patient.

If a drug is frequently used in single-patient INDs, FDA streamlines the process for obtaining permission. One example is thalidomide, a drug initially associated with birth defects in the 1950s but now being used experimentally to treat cancer. (FDA approved thalidomide in 1998 to treat leprosy.)

FDA has similar rules that give patients access to investigational new medical devices.

**A Difficult Decision**

All things being equal, is it worth it for a patient to get access to an experimental medication?

For society the additional safety information about the new drug may prove useful. And sometimes it does make a difference for individual patients. For example, people with AIDS who participated in the clinical trials for a category of drugs called protease inhibitors probably benefited because this class of drugs proved so dramatically effective. But for many other INDs, the success rates are much less impressive, such as tacrine (Cognex) for the treatment of Alzheimer's disease.

Even if access does not change long-term survival, it may provide for the patient and the family a sense that they are doing something and are not simply victims of some serious disease. Biomedical research advances rapidly and breakthroughs come from unexpected places, all feeding the hope that the next experimental drug will be the one that cures our ills.

*Larry Thompson is a member of FDA's public affairs staff.*

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## Finding Information About Investigational New Drugs

While finding and getting into an appropriate clinical trial for your individual disease is something like a scavenger hunt, the Internet has made it much easier to track down these studies. The following is a listing of major Internet sites where you can search for a clinical trial that may benefit you.

Information Program on Clinical Trials, (www.lhncbc.nlm.nih.gov/clin/) mandated by the FDA Modernization Act of 1997, is a joint FDA/National Institutes of Health resource. While initially containing only NIH studies, it will eventually include all federally and privately financed clinical studies.

CancerNet (http://cancernet.nci.nih.gov) is run by NIH's National Cancer Institute (NCI). It provides information on clinical trials. Information is also available through NCI's Cancer Information Service at 1-800-4-CANCER.

ACTIS (www.actis.org), the AIDS Clinical Trials Information Service, provides a wide range of information on current AIDS research, including drug trials, vaccine trials, and other educational material. Sponsored by the U.S. Public Health Service, including FDA, NIAID, Centers for Disease Control and Prevention, and the National Library of Medicine, ACTIS also can be reached at 1-800-TRIALS-A.

Information regarding clinical trials for rare disease can be found at http://rarediseases.info.nih.gov/, a database compiled by NIH's Office of Rare Diseases.

CenterWatch Clinical Trials Listing Service (www.centerwatch.com) is published on the Internet by CenterWatch Inc., a multimedia publishing company in Boston, Mass. It provides information on more than 5,000 active clinical trials as well as other information.

When a clinical trial is not an option, FDA facilitates access to an investigational new drug or an investigational medical device through other programs. For information on programs for, or access to, an unapproved investigational new drug, call FDA's Office of Special Health Initiatives at 301-827-4460.

*--L.T.*

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## Is The Risk Worth It?

No matter how promising a clinical trial or investigational new drug seems, there is no way to know

about all the risks before the study begins. While the hope is that the study will produce a cure, it's important to recognize that risks can prove significant. For example, in 1992, tests for a promising hepatitis B drug severely damaged the liver in 10 patients. Some died and others required liver transplants.

Because of these inherent uncertainties the health-care professionals conducting the study must ensure that the patient understands the risks as well as the benefits beforehand and is willing to proceed.

Here are some questions patients might want to ask to make sure they understand the consequences of entering a study or using an investigational new drug:

**1. What are the potential benefits from the treatment being studied? What have the animal or other human studies shown about the effectiveness of the drug?**
**2. What are the potential dangers from using this drug? Again, what do other animal and human studies show about the side effects?**
**3. In what phase is this clinical trial?**

Clinical trials are generally performed in three phases. A phase 1 trial is primarily designed to assess the safety profile in a small number of patients. Phase 2 tests the effectiveness of the treatment in a relatively small number of patients. Many drugs never progress beyond phase 2 because they are not effective. In phase 3, a large number of patients receive the drug to substantiate that the effectiveness seen in phase 2 is real and to work out the details of its use. Individual patients are most likely to benefit from drugs in the later phases of development.

**4. Will there be a control group?**

For a clinical trial to produce useful information, the group of patients receiving the new treatment needs to be compared with patients who receive something--or nothing--else. Often, patients in the control group receive whatever is the current standard therapy for the disease. Sometimes, the control group patients will receive a placebo--so-called sugar pills that produce no therapeutic benefit. In a clinical study, patients are randomly assigned to either the group treated with the experimental drug or to a group receiving the standard therapy or placebo.

**5. How do I know if I am eligible to be in the study?**

Every trial has a set of criteria to select the people that will be included in the study. These criteria generally relate to general health, stage of disease, and prior treatments and are designed to produce useful scientific information.

**6. Do I have to pay to be in a clinical study?**

Generally, studies funded by the federal government are free for the patient. Many studies funded by drug companies also do not cost anything. Some costs, however, may be paid by a patient's health insurance or managed-care plan.

**7. So I'm just a guinea pig, right?**

By the time most studies reach the stage where the new drug is being tested in people, a great deal is known about how it affects the body. While there is always the chance that something could go wrong, the safety of most drugs being studied is well understood. It is true, however, that researchers do not know if a treatment being studied works better than current therapies or not.

*--L.T.*

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# What FDA Does Not Do

Although FDA is responsible for overseeing the field of drug development, there are a number of

services the agency cannot provide to individual patients. For one thing, it cannot give out the name of drugs in development, a common request from patients who call the agency. Unless the company publicly releases information about the experimental treatment, FDA is currently forbidden to even acknowledge that it knows about the drug.

Along the same lines, FDA cannot make the drug available to individual patients or physicians. The agency simply does not have the product; only the company that is developing the drug has a supply. And FDA has no authority to require that the company make its drug available outside of the clinical trial.

FDA, itself, does not conduct any clinical trials or drug studies. The agency carries out its drug review and approval responsibilities by examining clinical and other data generated by the drug company.

And lastly, FDA does not give advice. While staff from the Office of Special Health Issues and the Center for Drug Evaluation and Research's drug information branch will often provide detailed information and explain the process for getting access to an experimental medication, the agency does not steer patients in one direction or the other. Information is provided so patients, in consultation with their physicians, can make their own informed decisions.

*--L.T.*

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*(Hypertext created by clb 1999-DEC-13)*

# EXHIBIT 2

# Guidance for Industry

## Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions

[PDF version of this document]

## DRAFT GUIDANCE
## This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Terry Toigo, 301-827-4460.

Additional copies are available from:

Office of Training and Communication
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
Tel) 301-827-4573
http://www.fda.gov/cder/guidance/index.htm

and/or

Office of Communication, Training and
Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
http://www.fda.gov/cber/guidelines.htm.
(Tel) Voice Information System at 800-835-4709 or 301-827-1800

**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research (CDER)**

**Center for Biologics Evaluation and Research (CBER)**
**January 2004**
**Procedural**

**Revision 1**

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# Guidance for Industry[1]

# Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions

**Contains Nonbinding Recommendations**

**Draft - Not for Implementation**

**This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.**

## I. INTRODUCTION

This guidance is intended to assist sponsors who will be submitting information to the Clinical Trials Data Bank. The data bank was established as required under section 113 of the Food and Drug Administration Modernization Act of 1997 (Modernization Act). This guidance updates and replaces the March 2002 guidance for industry of the same title to include assistance for sponsors who will be submitting information required by the Best Pharmaceuticals for Children Act (Public Law 107-109) (BPCA). Additional updates on procedural issues not related to the BPCA will be discussed in future revisions to this guidance.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

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## II. BACKGROUND

Section 113 of the Modernization Act creates a public resource for information on studies of drugs, including biological drug products, to treat serious or life-threatening diseases and conditions conducted under FDA's investigational new drug (IND) regulations (21 CFR part 312). Section 113 of the Modernization Act, enacted November 21, 1997, amends section 402 of the Public Health Service Act (42 U.S.C. 282). It directs the Secretary of Health and Human Services, acting through the Director of the National Institutes of Health (NIH), to establish, maintain, and operate a data bank of information on clinical trials for drugs to treat serious or life-threatening diseases and conditions. The Clinical Trials Data Bank is intended to be a central resource, providing current information on clinical trials to individuals with serious or life-threatening diseases or conditions, to other members of the public, and to health care providers and researchers. Specifically, section 113 of the Modernization Act requires that the Clinical Trials Data Bank contain (1) information about Federally and privately funded clinical trials for experimental treatments (drug and biological products) for patients with serious or life-threatening diseases or conditions, (2) a description of the purpose of each experimental drug, (3) patient eligibility criteria, (4) a description of the location of clinical trial sites, and (5) a point of contact for patients wanting to enroll in the trial. Section 113 of the Modernization Act requires that information provided through the Clinical Trials Data Bank be in a form that can be readily understood by the public. 42 U.S.C. 282(j)(3)(A).

The BPCA, signed by the President on January 4, 2002, requires a description of whether, and through what procedure, the manufacturer or sponsor of an IND will respond to requests for protocol exception, with appropriate safeguards, for single-patient and expanded access use of the investigational drug, particularly in children.

The NIH, through its National Library of Medicine (NLM) and with input from the FDA and others, developed the Clinical Trials Data Bank. The first version of the Clinical Trials Data Bank was made available to the public on February 29, 2000, on the Internet.[2] At that time, the data bank included primarily NIH-sponsored trials.

In response to the Modernization Act's requirements for a data bank, FDA made available two draft guidances and a final guidance. The first draft guidance provided recommendations for industry on the submission of protocol information to the Clinical Trials Data Bank.[3] It included information about the types of clinical trials for which submissions are required under section 113 of the Modernization Act, as well as the content of those submissions.

The second draft guidance addressed procedural issues, including how to submit required and voluntary protocol information to the Clinical Trials Data Bank, as well as issues related to submitting certification to the Secretary that disclosure of information for a particular protocol would substantially interfere with the timely enrollment of subjects in the clinical investigation.[4] The second draft guidance also proposed a time frame for submitting the information. A final guidance, made available on March 18, 2002,[5] combined the two draft guidances into a single guidance.

This updated guidance includes new recommended procedures for submitting details, as required by the BPCA, about single-patient use and expanded access use.

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## III. REQUIREMENTS UNDER SECTION 113 OF THE MODERNIZATION ACT FOR IND SPONSORS

### A. What information must I submit to the Clinical Trials Data Bank?

Section 113 of the Modernization Act requires you to submit information to the data bank about a clinical trial conducted under an investigational new drug (IND) application if it is for a drug to treat a serious or life-threatening disease or condition and it is a trial to test effectiveness (42 U.S.C. 282(j)(3)(A)). If you wish, you can also provide information on trials not designed to assess effectiveness or for drugs to treat conditions not considered serious or life-threatening.

Section 113 of the Modernization Act requires that you submit a description of the purpose of each experimental drug, patient eligibility criteria for participation in the trial, a description of the location of clinical trial sites, and a point of contact for those wanting to enroll in the trial. Section 113 requires that the data bank provide this information in a form that can be readily understood by members of the public (42 U.S.C. 282(j)(3)(A)).

The BPCA amended 42 U.S.C. 282 (j)(3)(A) to require that you submit a description of whether, and through what procedure, you (the manufacturer or sponsor of a clinical investigation of a new drug) will respond to requests for protocol exception, with appropriate safeguards, for single-patient and expanded access use of the investigational drug, particularly in children.[6]

To ensure that information available through the Clinical Trial Data Bank is in a form that is readily understood, we have established four data elements, which are listed below. The data elements are made up of the following data fields: (1) descriptive information, (2) recruitment information, (3) location and contact information, and (4) administrative data. We have established the Protocol Registration System (PRS), a Web-based data processing program, to facilitate collection of this information for the data bank. The four data elements, which are listed below, as well as definitions applicable to the PRS, can be viewed at http://prsinfo.clinicaltrials.gov/.

1. **Descriptive Information**

   Brief Title (in lay language)
   Brief Summary (in lay language)
   Study Design/Study Phase/Study Type
   Condition or Disease
   Intervention
   Single-patient/expanded access use

2. **Recruitment Information**

   Study Status Information including

   - Overall Study Status (e.g., recruiting, no longer recruiting)
   - Individual Site Status

   Eligibility Criteria/Gender/Age

3. **Location and Contact Information**

   Location of Trial
   Contact information (includes an option to list a central contact person for all trial sites)

4. **Administrative Data**

   Unique Protocol ID Number
   Study Sponsor
   Verification date

To verify the existence of an IND and to assist in administrative tracking, we ask that you also include in your submission the IND number and serial number and designate whether the IND is located in the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER). This administrative information is in a separate data field and will not be made public.

**B. When should I begin submitting clinical trial information?**

Section 113 of the Modernization Act requires that sponsors submit information no later than 21 days after the trial is opened for enrollment[7] (42 U.S.C. 282(j)(3)). Section 113 does not specify when sponsors must submit information about clinical trials that are existing and ongoing. To provide a transitional period for sponsors of clinical trials that are currently ongoing and expected to continue enrolling patients for more than 45 days, we ask that you submit information within 45 days after this guidance is made available through the *Federal Register*. We encourage you to submit information through the PRS for inclusion in the data bank as soon as possible.[8]

**C. Can I submit my information at specified intervals rather than on a rolling basis?**

As discussed above, you must submit information about new protocols open for enrollment within 21 days after the trial is open for enrollment (42 U.S.C. 282(j)(3)), and we request that you submit information about existing ongoing trials within 45 days after this guidance is published. Supplemental information can be submitted at 30-day intervals. Such information includes amendments to the protocol with respect to one of the data elements, or interruptions, continuations, or completion of enrollment for a study. Protocol changes related to eligibility or status information, such as routine opening and closing of trial sites, can be made at 30-day intervals. FDA strongly encourages you to update information about trials that are unexpectedly

closed (e.g., clinical hold) within 10 days after the closing or sooner if possible. To ensure that the information available through the data bank is timely and accurate, FDA also encourages you to review, verify, and update all active protocol records on a semi-annual basis, at a minimum.

**D. What is a trial for a serious or life-threatening disease or condition?**

FDA has defined serious and life-threatening diseases and conditions in previous documents. Most recently, FDA discussed issues related to products intended to treat serious or life-threatening diseases and conditions in the guidance for industry on *Fast Track Drug Development Programs - Designation, Development, and Application Review* (November 1998).[9] In that guidance, we stated that all conditions meeting the definition of life-threatening, as set forth at 21 CFR 312.81(a), would also be serious conditions. The term *life-threatening* is defined as (1) diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and (2) diseases or conditions with potentially fatal outcomes, where the endpoint of clinical trial analysis is survival (21 CFR 312.81(a)). All references in this document to serious diseases or conditions include life-threatening diseases and conditions.

As FDA reiterated in the *Fast Track Guidance*, the seriousness of a disease is a matter of judgment, but generally is based on such factors as survival, day-to-day functioning, and the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one. For example, acquired immunodeficiency syndrome (AIDS), all other stages of human immunodeficiency virus (HIV) infection, Alzheimer's disease, angina pectoris, heart failure, cancer, and many other diseases are clearly serious in their full manifestations. Furthermore, many chronic illnesses that are generally well managed by available therapy can have serious outcomes. For example, inflammatory bowel disease, asthma, rheumatoid arthritis, diabetes mellitus, systemic lupus erythematosus, depression, psychoses, and many other diseases can be serious in some or all of their phases or for certain populations.

Any investigational drug that has received fast track designation would be considered a drug to treat a serious disease or condition.[10] Information on effectiveness trials for drugs that have received fast track designation would qualify for submission to the Clinical Trials Data Bank.

**E. What is a trial to test effectiveness?**

Not all trials carried out under 21 CFR part 312 are trials to test effectiveness. FDA considers all phase 2, phase 3, and phase 4 trials with efficacy endpoints as trials to test effectiveness.[11]

**F. Which trials are provided to the public through the Clinical Trials Data Bank?**

Section 113 of the Modernization Act requires sponsors to submit information about clinical trials of experimental treatments for serious or life-threatening diseases and conditions when conducted under the IND regulations (42 U.S.C. 282(j)(3)(A)). Such information can be submitted at any time with the consent of the protocol sponsor, and must be submitted within 21 days after a trial to test effectiveness begins. In addition, section 113 of the Modernization Act states that information on all treatment IND protocols and all Group C protocols[12] must be included in the Clinical Trials Data Bank.

There are situations in which there may be patients with the disease or condition for which the drug is being developed who are not adequately treated by existing therapy, who do not meet the eligibility criteria for enrollment, or who are otherwise unable to participate in a controlled clinical study. In these situations, you may have initiated an expanded access protocol or be willing to provide the drug to an individual patient through a single-patient IND or protocol exception.[13] The BPCA requires that you submit a description of whether, and through what procedure, you will respond to requests for protocol exception for single-patient and expanded access use of the investigational drug, particularly in children.

For protocols not specifically mentioned above, sponsors should review each protocol submitted to an IND to determine if the protocol is for a serious disease or condition and if it is a trial to test effectiveness. If the protocol meets these criteria, the sponsor must submit information about the trial to the Clinical Trials Data Bank, ***unless*** the sponsor provides detailed certification to FDA that such a disclosure would substantially interfere with the timely enrollment of subjects in the investigation (42 U.S.C. 282(j)(3) and (j)(4)). Sponsors with questions on whether protocols meet the criteria for submission to the Clinical Trials Data Bank are encouraged to contact the appropriate review division for additional guidance.

**G. Must I include information about foreign trial sites?**

Yes, you must include information about foreign trials when those trials are conducted under an IND submitted to FDA and the trial meets the criteria for submission to the Clinical Trials Data Bank. Section 113 of the Modernization Act requires sponsors to submit information about specified clinical trials that are "under regulations promulgated pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act," which are FDA's IND regulations (42 U.S.C. 282(j)(3)). Sponsors may voluntarily conduct a foreign trial under the IND regulations. Sponsors are not required to submit information to the Clinical Trials Data Bank when a foreign trial is not conducted under an IND.

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## IV. IMPLEMENTATION ISSUES

**A. How do I submit information to the Clinical Trials Data Bank?**

To facilitate the submission process, we have established the Web-based PRS at *ClinicalTrials.gov*. The system allows for entry of required and voluntary information about clinical trials. You or your designee can initiate submission of clinical trial information to *ClinicalTrials.gov* by completing a registration form at http://prsinfo.clinicaltrials.gov/. After you have entered the data, the PRS generates a receipt for use by sponsors. An electronic copy of the receipt will be sent to the FDA.

**B. What information about trial sites must be included?**

Section 113 of the Modernization Act requires sponsors to submit a description of the location of trial sites and a point of contact. To ensure an adequate description, we recommend that you provide for each individual trial site the full name of the organization, city, state, postal code, and country where the protocol is being conducted; and a central contact name and phone number. You can also provide the names and phone numbers of individual site contacts.

**C. How long does it take for information to be made available on ClinicalTrials.gov?**

Studies will be made available to the public through ClinicalTrials.gov within 2 to 5 days after submission by the sponsor.

**D. How long will information about studies remain available through ClinicalTrials.gov?**

NLM intends to maintain the Data Bank as a long-term registry of clinical trials. Therefore, in addition to information about open trials, information about closed trials will also be available through *ClinicalTrials.gov*, even after accrual and analysis are completed and the product is approved.

**E. Can information be transferred from a sponsor computer to the PRS?**

Yes. Information can be transferred according to the format specified by the PRS. The PRS has a mechanism for uploading and downloading XML-formatted protocol records. Instructions for transferring information are provided at http://prsinfo.clinicaltrials.gov/

**F. Can intermediaries acting on behalf of a sponsor submit data?**

Yes. For example, in some cases a sponsor might want to contract with an information management company to serve as an intermediary in preparing data for inclusion in ClinicalTrials.gov. The information management company, when authorized by the sponsor, could act on behalf of the sponsor for this purpose.

**G. Can sponsors designate multiple individuals to be data providers?**

Yes. When sponsors register to become a PRS data provider, they will be given information, including instructions, for creating additional users for their accounts. A sponsor can control access to the account by designating users and administrators for the account.

**H. What happens to the information submitted to the Clinical Trials Data Bank?**

Except for the IND number, serial number, and FDA center designation, all information submitted through the PRS is made available to the public at http://clinicaltrials.gov.

**I. Can I submit other information to the Clinical Trials Data Bank?**

Yes. PRS is designed to permit you to submit more detailed information about a protocol. Additional data fields (e.g., projected enrollment) and their definitions are included in the PRS. You also can submit protocol information about other clinical trials under IND, including trials for a disease or condition that is not serious or any trial that is not designed to test effectiveness. Finally, you can submit information about results of a trial. This information, which, according to the structure of the Clinical Trials Data Bank, is to come from the published literature, should be linked by including the unique MEDLINE identifier for citations of publications. You can use the *link* section provided to allow pointers to Web pages directly relevant to the protocol. If you link to other Web pages from your entries, you should ensure that the links do not misbrand your products, for example, by promoting the products before the product or an indication is approved. (See 21 U.S.C. 321(n), 331(a)(b)(c)(d), 352(a)(n) http://www.fda.gov/opacom/laws/fdcact/fdcact1.htm.) When inputting links to other web pages, the database will instruct you that the links should be directly relevant to the protocol, and that you should not link to sites whose primary goal is to advertise or sell commercial products or services.

**J. Should I continue submitting information to the ACTIS and PDQ databases?**

No. All information for AIDS and cancer protocols that meet the requirements of section 113 of the Modernization Act must now be submitted to ClinicalTrials.gov through the PRS. Data from the current AIDS Clinical Trials Information System (ACTIS) and Physician's Data Query (PDQ) databases are included in *ClinicalTrials.gov*. Information from the Rare Diseases and National Institute of Aging Databases is also included in *ClinicalTrials.gov*.

**K. Are there exemptions for submitting clinical trials information?**

Information about an investigation will not be included in the data bank if you provide a detailed certification to the Secretary of Health and Human Services that disclosure of such information would substantially interfere with timely enrollment of subjects in the clinical trial and the

Secretary does not disagree. If there is disagreement, the Secretary will provide a detailed written determination that such disclosure would not substantially interfere with such enrollment (42 U.S.C. 282(j)(4)).

FDA has not identified specific instances when disclosure of information would substantially interfere with enrollment of subjects in a clinical investigation. We solicited comments on this topic for the purpose of including a listing of acceptable reasons for certification in the final guidance. We received no comments. Therefore, if you identify a specific instance when disclosure of information would interfere with enrollment of subjects in a clinical investigation, FDA will consider your request on a case-by-case-basis.

All requests for exemption should be forwarded to Director, Office of Special Health Issues, Office of Communications and Constituent Relations, Office of the Commissioner, HF-12, 5600 Fishers Lane Rockville, MD 20857, or by email at 113trials@oc.fda.gov, or by fax at 301-443-4555.

### L. Is Institutional Review Board preapproval of the protocol listing required?

No. Section 113 of the Modernization Act does not require prior IRB approval when submitting this information to the Clinical Trials Data Bank. Current FDA guidance recommends that IRB review of listings need not occur when, as here, the system format limits the information provided to basic information, such as title, purpose of the study, protocol summary, basic eligibility criteria, study site locations, and how to contact the site for further information.[14]

### M. Will FDA monitor compliance?

A copy of the protocol listing in ClinicalTrials.gov will be sent to the FDA. FDA's Office of Special Health Issues initiated a pilot educational program in 2002 that included a component to evaluate compliance. The primary objective of the pilot program is to educate sponsors about the existence of the guidance document and the availability of the online PRS data entry tool. The secondary objective of the pilot program is to evaluate the success of the educational initiative. The pilot program will measure the number of protocols (voluntary and required) made available through the *ClinicalTrials.gov* database. Data from the completed project will help senior FDA officials assess the need for further efforts to facilitate or perhaps compel participation in *ClinicalTrials.gov*.

### N. What information about protocol exceptions, single-patient use, and expanded access protocols must I include?

There are situations in which there may be patients with the disease or condition for which the drug is being developed who are not adequately treated by existing therapy, who do not meet the eligibility criteria for enrollment, or who are otherwise unable to participate in a controlled clinical study. In such a situation, you may wish to provide the drug to a patient through a protocol exception/exemption, single patient IND, or expanded access protocol.

The BPCA amended Section 113 of the Modernization Act to require that you submit, in addition to the information already included in the Clinical Trials Data Bank, a description of whether and through what procedure you will respond to requests for protocol exception, with appropriate safeguards, for single-patient and expanded access use of the investigational drug, particularly in children.

The PRS includes a mechanism for providing information about protocol exceptions, single-patient INDs, and expanded access protocols. In order to comply with the BPCA amendment to section 113 of the Modernization Act, we suggest that you address the following two questions and provide a brief description as described below. This information is required for each new protocol that is listed in the data bank; we encourage you also to provide this information for

protocols currently open to enrollment.

- Is this investigational drug available for use in adults through a protocol exception, single-patient IND, or expanded access protocol?
  Yes No

- Is this investigational drug available for use in children through a protocol exception, single-patient IND, or expanded access protocol?
  Yes No

- Brief description of the procedure for responding to requests for expanded access, including contact number and/or email address.

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[1] This guidance has been prepared by the Implementation Team for section 113 of the Food and Drug Administration Modernization Act of 1997, including individuals from the Office of the Commissioner, the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Center for Devices and Radiological Health (CDRH), at the Food and Drug Administration.

**Paperwork Reduction Act Public Burden Statement:** According to the Paperwork Reduction Act of 1995, a collection of information should display a valid OMB control number. The valid OMB control number for this information collection is 0910-0459 (expires 03/31/2004). The time to complete this information collection is estimated to average 284 hours per response, including the time to review instructions, search existing data resources, gather the data needed, and complete and review the information collection.

[2] See http://clinicaltrials.gov

[3] See http://www.fda.gov/OHRMS/DOCKETS/98fr/001033gl.pdf

[4] See 66 FR 35798 and http://www.fda.gov/OHRMS/DOCKETS/98fr/001033gd.pdf

[5] See 67 FR 12022 and http://www.fda.gov/OHRMS/DOCKETS/98fr/00d-1033_gdl0003.pdf FINAL

[6] See 42 U.S.C. 282(j)(3)(A) at http://www.fda.gov/opacom/laws/pharmkids/contents.html.

[7] Section 113 says "not later than 21 days after the approval of the protocol." Because the Agency does not approve protocols, we have interpreted this to mean within 21 days after the trial is open for enrollment.

[8] See http://prsinfo.clinicaltrials.gov.

[9] CDER guidances are available at http://www.fda.gov/cder/guidance/index.htm.

[10] That a drug is intended to treat a serious or life-threatening disease or condition, however, does not mean that it fills an unmet medical need and qualifies for fast track designation under section 506 of the Food Drug and CosmeticAct (21 U.S.C. 356).

[11] Listing a trial in the Clinical Trials Data Bank is not a guarantee that the trial design is considered adequate to support approval of a drug, nor does it reflect any judgment on the conduct, analysis, or outcome of the study.

[12] "Group C protocols" refers to investigational drugs designated by FDA for the treatment of specific cancers. These drugs have reproducible efficacy in one or more specific tumor types. Such a drug has altered or is likely to alter the pattern of treatment of disease and can be safely administered by properly trained physicians without specialized supportive care facilities. See National Cancer Institute Handbook for Investigators, Appendix XV, "Policy for Group C Drug Distribution," http://ctep.info.nih.gov/HandbookText/Appendix_XV.htm#Proc_Mgmt_GrpC_Prot.

[13] There are a number of mechanisms FDA has used to provide access to promising investigational therapies. In addition to treatment INDs and treatment protocols, which are described in FDA regulations, expanded access mechanisms fall under a variety of terms, such as single patient INDs, emergency INDs, protocol exemptions, special exceptions, open label extensions, and parallel track. FDAMA has codified certain FDA regulations and practices regarding expanded patient access to experimental drugs. FDA is reviewing current regulations and practices to assure coordination with FDAMA.

[14] The 1998 update of *Information Sheets: Guidance for Institutional Review Boards and Clinical Investigators* provides guidance on IRB review and approval of listings of clinical trials on the Internet. See http://www.fda.gov/oc/ohrt/irbs/toc4.html#recruiting.

Updated January 26, 2004

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# EXHIBIT 3

the FAA proposes to amend 14 CFR part 39 as follows:

## PART 39—AIRWORTHINESS DIRECTIVES

1. The authority citation for part 39 continues to read as follows:

**Authority:** 49 U.S.C. 106(g), 40113, 44701.

**§ 39.13 [Amended]**

2. The Federal Aviation Administration (FAA) amends § 39.13 by adding the following new airworthiness directive (AD):

**Airbus:** Docket No. FAA–2006–26120; Directorate Identifier 2006–NM–184–AD.

**Comments Due Date**

(a) The FAA must receive comments on this AD action by January 16, 2007.

**Affected ADs**

(b) None.

**Applicability**

(c) This AD applies to all Airbus Model A300 B4–601, B4–603, B4–620, and B4–622 airplanes; Model A300 B4–605R and B4–622R airplanes; Model A300 F4–605R and F4–622R airplanes; and Model A300 C4–605R Variant F airplanes; certificated in any category.

**Note 1:** This AD requires revisions to certain operator maintenance documents to include new inspections and critical design configuration control limitations (CDCCLs). Compliance with the operator maintenance documents is required by 14 CFR 91.403(c). For airplanes that have been previously modified, altered, or repaired in the areas addressed by these inspections and CDCCLs, the operator may not be able to accomplish the inspections and CDCCLs described in the revisions. In this situation, to comply with 14 CFR 91.403(c), the operator must request approval for an alternative method of compliance according to paragraph (j) of this AD. The request should include a description of changes to the required inspections and CDCCLs that will preserve the critical ignition source prevention feature of the affected fuel system.

**Unsafe Condition**

(d) This AD results from fuel system reviews conducted by the manufacturer. We are issuing this AD to prevent the potential of ignition sources inside fuel tanks, which, in combination with flammable fuel vapors caused by latent failures, alterations, repairs, or maintenance actions, could result in fuel tank explosions and consequent loss of the airplane.

**Compliance**

(e) You are responsible for having the actions required by this AD performed within the compliance times specified, unless the actions have already been done.

**Revise Airworthiness Limitations Section (ALS) To Incorporate Fuel Maintenance and Inspection Tasks**

(f) Within 3 months after the effective date of this AD, revise the ALS of the Instructions for Continued Airworthiness to incorporate Airbus A300–600 ALS Part 5—Fuel Airworthiness Limitations, dated May 31, 2006, as defined in Airbus A300–600 Fuel Airworthiness Limitations, Document 95A.1929/05, Issue 1, dated December 19, 2005 (approved by the European Aviation Safety Agency (EASA) on March 13, 2006), Section 1, "Maintenance/Inspection Tasks." For all tasks identified in Section 1 of Document 95A.1929/05, the initial compliance times start from the effective date of this AD and must be accomplished within the repetitive interval specified in Section 1 of Document 95A.1929/05, except as provided by paragraph (g) of this AD.

**Initial Compliance Time for Task 28–18–00–03–1**

(g) For Task 28–18–00–03–1, "Operational check of lo-level/underfull/calibration sensors," identified in Section 1, "Maintenance/Inspection Tasks," of Airbus A300–600 Fuel Airworthiness Limitations, Document 95A.1929/05, Issue 1, dated December 19, 2005: The initial compliance time is the later of the times specified in paragraphs (g)(1) and (g)(2) of this AD. Thereafter, Task 28–18–00–03–1 must be accomplished within the repetitive interval specified in Section 1 of Document 95A.1929/05.

(1) Prior to the accumulation of 34,000 total flight hours.

(2) Within 72 months or 20,000 flight hours after the effective date of this AD, whichever occurs first.

**Revise ALS To Incorporate CDCCLs**

(h) Within 12 months after the effective date of this AD, revise the ALS of the Instructions for Continued Airworthiness to incorporate Airbus A300–600 ALS Part 5—Fuel Airworthiness Limitations, dated May 31, 2006, as defined in Airbus A300–600 Fuel Airworthiness Limitations, Document 95A.1929/05, Issue 1, dated December 19, 2005 (approved by the EASA on March 13, 2006), Section 2, "Critical Design Configuration Control Limitations."

**No Alternative Inspections, Inspection Intervals, or CDCCLs**

(i) Except as provided by paragraph (j) of this AD: After accomplishing the actions specified in paragraphs (f) and (h) of this AD, no alternative inspections, inspection intervals, or CDCCLs may be used.

**Alternative Methods of Compliance (AMOCs)**

(j)(1) The Manager, International Branch, ANM–116, Transport Airplane Directorate, FAA, has the authority to approve AMOCs for this AD, if requested in accordance with the procedures found in 14 CFR 39.19.

(2) Before using any AMOC approved in accordance with § 39.19 on any airplane to which the AMOC applies, notify the appropriate principal inspector in the FAA Flight Standards Certificate Holding District Office.

**Related Information**

(k) EASA airworthiness directive 2006–0201, dated July 11, 2006, also addresses the subject of this AD.

Issued in Renton, Washington, on October 17, 2006.

**Jeffrey E. Duven,**

*Acting Manager, Transport Airplane Directorate, Aircraft Certification Service.*

[FR Doc. E6–21262 Filed 12–13–06; 8:45 am]

BILLING CODE 4910–13–P

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

### 21 CFR Part 312

**[Docket No. 2006N–0062]**

**RIN 0910–AF14**

### Expanded Access to Investigational Drugs for Treatment Use

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Proposed rule.

**SUMMARY:** The Food and Drug Administration (FDA) is proposing to amend its regulations on access to investigational new drugs for the treatment of patients. The proposed rule would clarify existing regulations and add new types of expanded access for treatment use. Under the proposal, expanded access to investigational drugs for treatment use would be available to individual patients, including in emergencies; intermediate-size patient populations; and larger populations under a treatment protocol or treatment investigational new drug application (IND). The proposed rule is intended to improve access to investigational drugs for patients with serious or immediately life-threatening diseases or conditions, who lack other therapeutic options and who may benefit from such therapies.

**DATES:** Submit written or electronic comments by March 14, 2007. Submit written comments on the information collection requirements by January 16, 2007.

**ADDRESSES:** You may submit comments, identified by Docket No. 2006N–0062 and RIN 0910–AF14, by any of the following methods:

*Electronic Submissions*

Submit electronic comments in the following ways:

- Federal eRulemaking Portal: *http://www.regulations.gov*. Follow the instructions for submitting comments.
- Agency Web site: *http://www.fda.gov/dockets/ecomments*.

Follow the instructions for submitting comments on the agency Web site.

*Written Submissions*

Submit written submissions in the following ways:

- FAX: 301–827–6870.
- Mail/Hand delivery/Courier [For paper, disk, or CD–ROM submissions]: Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

To ensure more timely processing of comments, FDA is no longer accepting comments submitted to the agency by e-mail. FDA encourages you to continue to submit electronic comments by using the Federal eRulemaking Portal or the agency Web site, as described in the *Electronic Submissions* portion of this paragraph.

*Instructions*: All submissions received must include the agency name and docket number and Regulatory Information Number (RIN) for this rulemaking. All comments received may be posted without change to *http://www.fda.gov/ohrms/dockets/default.htm*, including any personal information provided. For additional information on submitting comments, see the "Comments" heading of the **SUPPLEMENTARY INFORMATION** section of this document.

*Docket*: For access to the docket to read background documents or comments received, go to *http://www.fda.gov/ohrms/dockets/default.htm* and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

The Office of Management and Budget (OMB) is still experiencing significant delays in the regular mail, including first class and express mail, and messenger deliveries are not being accepted. To ensure that comments on the information collection are received, OMB recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB, Attn: Desk Officer for FDA, FAX: 202–395–6974.

**FOR FURTHER INFORMATION CONTACT:** Colleen L. Locicero, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, rm. 4200, Silver Spring, MD 20993–0002, 301–796–2270; or Steve Ripley, Center for Biologics Evaluation and Research (HFM–17), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852, 301–827–6210.

**SUPPLEMENTARY INFORMATION:**

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## I. Background

### *A. Informal Access to Drugs for Treatment Use*

FDA has a long history of permitting access to investigational drugs to treat serious or immediately life-threatening diseases or conditions without adequate available therapy under INDs, generally for drugs being evaluated in clinical studies intended to support marketing. The distinction between these and the usual studies covered under an IND is that the treatment uses are not primarily to answer safety or effectiveness questions about the drug, but are intended to treat the patient. Before 1987, there was no formal recognition of such treatment use in the IND regulations, but investigational drugs were made available for treatment use informally. "Compassionate use INDs," "single-patient protocol exceptions," and "large open protocols" are some of the terms that have been used to refer to such informal access. The vast majority of these INDs were used to make an investigational drug available to an individual patient, but some of the expanded access programs made particularly promising investigational drugs available to large populations. For example, more than 10,000 patients obtained access through treatment access programs to the first cardioselective beta-blockers and the first calcium channel blockers for vasospastic angina.

### *B. Current Regulations Concerning Expanded Access for Treatment Use*

In 1987, FDA revised the IND regulations in part 312 (21 CFR part 312) to explicitly provide for one specific kind of treatment use of investigational drugs (52 FR 19466, May 22, 1987). Section 312.34 authorizes broad access to investigational drugs under a treatment protocol or treatment IND when the following criteria are met:

- The drug is intended to treat a serious or immediately life-threatening disease;
- There is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease in the intended patient population;
- The drug is under investigation in a controlled clinical trial under an IND in effect for the trial, or all clinical trials have been completed; and
- The sponsor of the controlled clinical trial is actively pursuing marketing approval of the investigational drug with due diligence.

Section 312.34 states that for a serious disease, data from phase 3 trials or, in appropriate circumstances, data from phase 2 trials would ordinarily be needed to permit treatment use in a substantial population. For an immediately life-threatening disease, less evidence of safety and effectiveness is needed for treatment use. The standard for treatment use for immediately life-threatening conditions is that the available scientific evidence, taken as a whole, provides a reasonable basis to conclude that the drug may be effective and would not expose patients to an unreasonable and significant additional risk of illness or injury. FDA estimates that more than 100,000 patients have received investigational drugs through treatment INDs.

The 1987 IND regulations recognized only one kind of treatment use, the treatment protocol or treatment IND, generally providing availability to a broad population. However, it also implicitly acknowledged the existence of other kinds of treatment use, notably use in individual patients, by adding a provision describing an expedited procedure to obtain an investigational drug for treatment use in an emergency

situation (§ 312.36). However, § 312.36 does not describe criteria or requirements that must be met to authorize individual patient treatment use.

*C. Concerns About Treatment Use Programs*

FDA has been criticized for its failure to explain in regulation or guidance the basis for agency decisionmaking on individual patient treatment use and other treatment use programs not currently described in FDA's regulations. One concern is that the lack of specific criteria and submission requirements results in disparate access to treatment use for different types of patients and diseases. Some have asserted that knowledge of FDA's policies on these other kinds of treatment use tends to be concentrated among physicians in academic medical centers who are familiar with investigational drugs and FDA procedures. Consequently, according to this line of criticism, patients treated outside of academic medical centers are less likely to have access to investigational drugs for treatment use. There has also been concern that access to investigational drugs for treatment use has focused primarily on cancer- and human immunodeficiency virus (HIV)-related conditions, and that patients with other types of serious diseases or conditions have not had comparable access to appropriate treatment use of unapproved drugs.

*D. The Food and Drug Administration Modernization Act of 1997*

In response to these concerns about inconsistent policies, inequitable access, and preferential access for certain categories of disease, in the Food and Drug Administration Modernization Act of 1997 (FDAMA) (Public Law 105–115), Congress amended the Federal Food, Drug, and Cosmetic Act (the act) to include specific provisions concerning expanded access to investigational drugs for treatment use (Expanded Access to Unapproved Therapies and Diagnostics, section 561 (21 U.S.C. 360bbb) of the act). By incorporating specific expanded access provisions in the statute, Congress intended to emphasize that "opportunities to participate in expanded access programs are available to every individual with a life-threatening or seriously debilitating illness for which there is not an effective, approved therapy" (Joint Explanatory Statement of the Committee of Conference in House Report 105–399, November 9, 1997, p. 100).

Section 561(a) of the act provides specific statutory authority to make investigational drugs available for the diagnosis, monitoring, or treatment of a serious disease or condition in an emergency situation. The Secretary of Health and Human Services (the Secretary) is to determine appropriate conditions under which an investigational drug may be made available in an emergency situation.

Section 561(b) of the act permits any person, acting through a licensed physician, to request access to an investigational drug to diagnose, monitor, or treat a serious disease or condition provided that the following conditions are met:

- The licensed physician determines that the person has no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition, and that the probable risk from the investigational drug is not greater than the probable risk from the disease or condition;
- The Secretary determines that there is sufficient evidence of safety and effectiveness to support the use of the investigational drug;
- The Secretary determines that provision of the investigational drug will not interfere with the initiation, conduct, or completion of clinical investigations to support marketing approval; and
- The sponsor or clinical investigator submits a protocol consistent with the requirements of section 505(i) of the act (21 U.S.C 355(i)) and its implementing regulations in part 312, which describe use of the drug in a single patient or a small group of patients.

Section 561(c) of the act closely tracks existing § 312.34 of the IND regulations. Section 561(c) authorizes the Secretary to permit an investigational drug to be made available for widespread access if the following determinations have been made:

1. The investigational drug is intended for use in the diagnosis, monitoring, or treatment of a serious or immediately life-threatening disease or condition;
2. There is no comparable or satisfactory alternative therapy available to diagnose, monitor, or treat that stage of disease or condition in a particular patient population;
3. The investigational drug is under investigation in a controlled clinical trial under an IND, or all clinical trials necessary for approval of the use have been completed;
4. The sponsor of the controlled clinical trial is actively pursuing marketing approval with due diligence;
5. The provision of the investigational drug will not interfere with the enrollment of patients in ongoing clinical investigations;
6. In the case of serious diseases, there is sufficient evidence of safety and effectiveness to support the use;
7. In the case of immediately life-threatening diseases, the available scientific evidence, taken as a whole, provides a reasonable basis to conclude that the investigational drug may be effective for its intended use and would not expose patients to an unreasonable and significant risk of illness or injury.

Section 561(c) also provides that a protocol for an expanded access treatment IND shall be subject to the requirements of section 505(i) of the act and FDA's implementing regulations in part 312.

To specifically address concerns that physicians and their patients are often unaware of the availability of investigational drugs under access programs, section 561(c) of the act also allows the Secretary to inform national, State, and local medical associations and societies, voluntary health associations, and other appropriate persons about the availability of expanded access treatment INDs or treatment protocols.

## II. Why FDA Is Proposing This Rule

This proposed rule is intended to further address the concerns that motivated Congress to include in the act specific provisions on expanded access to investigational drugs for treatment use. As discussed in section I of this document, these concerns included inconsistent application of access policies and programs and inequities in access based on the relative sophistication of the setting in which a patient is treated or on the patient's disease or condition. By describing in detail in the proposed rule the criteria, submission requirements, and safeguards for the different types of expanded access for treatment uses of investigational drugs, the agency seeks to increase awareness and knowledge of expanded access programs and the procedures for obtaining investigational drugs. Increased knowledge and awareness about expanded access options should make investigational drugs more widely available in appropriate situations. Clearly articulated procedures for obtaining investigational drugs for treatment use should ease the administrative burdens on individual physicians seeking investigational drugs for their patients, as well as the burdens on sponsors who make investigational drugs available for treatment use. In addition, we expect

that clearly articulating procedures and standards for expanded access will result in more patients with serious or immediately life-threatening diseases or conditions getting the earliest possible access to these therapies.

## III. Goals and Limitations of the Proposed Rule

Recognizing that FDA's authority derives from the act, the proposed rule attempts to reconcile individual patients' desires to make their own decisions about their health care with society's need for drugs to be developed for marketing. It recognizes the need for the risks and benefits of drugs to be well characterized and the need for appropriate protection of human subjects in an investigation. These interests are not always easily reconciled. Allowing individual patients relatively unfettered access to an investigational drug at a preliminary stage in its development, for example, may expose them to significant and unacceptable risks.

In addition, patients may find participation in a clinical trial less desirable than receiving the drug for treatment use for a variety of reasons. For example, clinical trial participants may receive a treatment other than the study drug, and clinical trials may have more onerous monitoring requirements (such as laboratory and other tests). Thus, a system of blindly permitting uncontrolled access to investigational drugs could make it difficult or impossible to enroll adequate numbers of patients in clinical trials to establish the safety and effectiveness of the drug for marketing approval.

FDA has a statutory responsibility to ensure that marketed drugs are safe and effective, and its rules should not compromise the integrity of the drug development process. In this proposed rule, as envisioned by the act, the agency has tried to strike the appropriate balance between authorizing access to promising drugs for treatment use under our expanded access authority and ensuring the integrity of the drug approval process.

While this proposed rule aims to clarify, and thereby expand, the situations in which expanded access to unapproved drugs could be available, under its existing authority, FDA cannot compel a drug manufacturer to provide access to investigational drugs for treatment use.

## IV. Description of the Proposed Rule

FDA is proposing to amend its regulations on INDs by removing the current sections on treatment use, revising the section on clinical holds, and adding subpart I on expanded access. The term "expanded access" is used here to refer to all types of treatment uses. The term "treatment protocol or treatment IND" continues to refer to one specific kind of treatment use, the large access protocol.

### *A. Sections Removed*

The proposed rule would remove the following three sections of FDA's regulations:

- Current § 312.34 concerning the treatment use of an investigational new drug;
- Current § 312.35 concerning submissions for treatment use; and
- Current § 312.36 concerning emergency use of an investigational new drug.

### *B. Clinical Holds*

The proposed rule would amend § 312.42 *Clinical holds and requests for modification* by providing for clinical holds, when necessary, of any of the types of expanded access uses described in this proposed rule. A clinical hold is an order issued by FDA to the sponsor to delay a proposed clinical investigation or suspend an ongoing investigation (§ 312.42(a)). Proposed § 312.42(b)(3)(i) provides that FDA may place an expanded access IND or protocol[1] on clinical hold if it is determined that the pertinent criteria in proposed subpart I for permitting the expanded access use to begin are not satisfied or the IND or protocol does not comply with the requirements for expanded access submissions in proposed subpart I.

Proposed § 312.42(b)(3)(ii) provides that FDA may place an ongoing expanded access IND or protocol on clinical hold if it is determined that the pertinent criteria in proposed subpart I for permitting the expanded access are no longer satisfied (e.g., a satisfactory alternative therapy becomes available).

### *C. Expanded Access Overview*

The agency is proposing to add new subpart I to part 312. Proposed subpart I describes the following ways that expanded access to treatment use of investigational drugs would be available:

- Expanded access for individual patients, including emergency procedures;
- Expanded access for intermediate-size patient populations (smaller than those typical of a treatment IND or treatment protocol); and
- Expanded access treatment IND or treatment protocol (described in current §§ 312.34 and 312.35).

The following items are set forth in the proposed rule: (1) Criteria that must be met to authorize the expanded access use, (2) requirements for expanded access submissions, and (3) safeguards to protect patients and preserve the ability to develop meaningful data about treatment use.

### *D. General Provisions*

Proposed § 312.300(a) states that the aim of subpart I is to facilitate the availability of investigational new drugs to seriously ill patients when there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the patient's disease or condition. Proposed § 312.300(b) provides a definition of the term "immediately life-threatening disease" as a stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.

### *E. Requirements for All Expanded Access Uses (Proposed § 312.305)*

Proposed § 312.305 contains the general requirements for the use of investigational drugs when the primary purpose is to diagnose, monitor, or treat a patient's disease or condition, rather than to generate safety and effectiveness data to support a marketing application. Proposed § 312.305 contains criteria, submission requirements, and safeguards that apply to all expanded access uses described in proposed subpart I. Additional criteria, submission requirements, and safeguards that apply to specific types of expanded access use are described in the sections of the proposed rule describing those expanded access types.

#### 1. Criteria for All Expanded Access Uses

Proposed § 312.305(a) sets forth three criteria that apply to all types of expanded access use:

a. *First criterion.* Under proposed § 312.305(a)(1), FDA must determine that the patient (or patients) to be treated has a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition. Because, by definition, the risks and benefits of investigational drugs are not as well characterized as those of approved drugs, the agency believes, and the act contemplates, that expanded access to investigational

[1] A submission seeking to allow an expanded access use of an investigational drug may come to FDA either in the form of a new, separate IND or as a new protocol submitted to an already existing IND.

drugs is warranted only under these conditions. Section 561(c)(1) and (c)(2) of the act expressly requires FDA to make these determinations in order to authorize a treatment IND or treatment protocol, and section 561(b)(1) and (b)(2) of the act likewise requires FDA to determine that there is sufficient evidence of safety and effectiveness to support the use of the unapproved drug in treating an individual patient or a small group of patients. Determining that the patient has a serious or immediately life-threatening disease or condition and that there is no comparable or satisfactory alternative therapy are integral parts of determining whether there is sufficient evidence of safety and effectiveness to support the proposed use in the situation described by the physician or sponsor seeking the authorization.

In various documents, the agency has described or illustrated what is meant by a serious condition (see, e.g., FDA's guidance for industry entitled "Fast Track Drug Development Programs—Designation, Development, and Application Review" (63 FR 64093, November 18, 1998), revised 2004, pp. 3–4; preamble to the 1992 proposed rule on accelerated approval of new drugs for serious or life-threatening illnesses (57 FR 13234 at 13235, April 15, 1992)). As discussed in these documents, the "serious disease or condition" requirement refers to conditions that have an important effect on functioning (e.g., stroke, schizophrenia, rheumatoid arthritis, osteoarthritis) or on other aspects of quality of life (e.g., chronic depression, seizures). Alzheimer's dementia, Amyotrophic Lateral Sclerosis (ALS), and narcolepsy are specific examples of serious conditions for which FDA has granted expanded access to investigational drugs in the past. Short-lived and self-limiting morbidity will usually not be sufficient to qualify a condition as serious, but the morbidity need not be irreversible, provided it is persistent or recurrent. Similarly, the proposed requirement here that treatment be for a "serious disease or condition" is not intended to be unnecessarily restrictive. It is primarily intended to exclude expanded access to investigational drugs for conditions that are clearly not serious (e.g., symptomatic relief of minor pain or allergic symptoms and other self-limiting conditions not associated with major morbidity). Because of the difficulty of specifically describing the criteria that characterize a "serious disease or condition," the proposed rule itself does not provide a definition of "serious," though it does provide a definition of "immediately life-threatening." See proposed § 312.300(b). We solicit comments on this approach. If a disease or condition were to be both serious and immediately life-threatening, for the purpose of this proposed rule, it would be considered "immediately life-threatening."

Ordinarily, a lack of comparable or satisfactory therapeutic alternatives would mean that there exists no other available therapy to treat the patient's condition or that the patient has tried available therapies and failed to respond adequately or is intolerant to them. Available therapy, as defined in FDA's guidance for industry entitled "Available Therapy" (69 FR 44039, July 23, 2004), generally refers to FDA-approved products that are labeled to be used for the relevant disease or condition. In some cases, however, available therapy might mean a treatment that is not regulated by FDA (e.g., surgery) or one that is not labeled for use for the relevant disease or condition, but is supported by compelling literature evidence.

b. *Second criterion.* Under proposed § 312.305(a)(2), FDA must determine that the potential patient benefit justifies the potential risks of the treatment use and that those potential risks are not unreasonable in the context of the disease or condition to be treated. FDA is required to make this determination under sections 561(b)(2), (c)(6), and (c)(7) of the act.

c. *Third criterion.* Under proposed § 312.305(a)(3), FDA must determine that providing the investigational drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use. Section 561(b)(3) and (c)(5) of the act requires FDA to make this determination. The most efficient and effective way to make a drug available to all those who can benefit from the drug, is to market it. Therefore, it is important to ensure that expanded access use does not compromise enrollment in the trials needed to demonstrate the safety and effectiveness of the drug.

Proposed § 312.305(a) does not elaborate on the safety and/or effectiveness showing that must be made to merit authorization of the expanded access use. Rather, the showing is described in the criteria that pertain to each type of expanded access because the evidence needed to demonstrate the safety and potential benefit of a proposed use varies with the size of the population to be treated and the relative seriousness of the disease or condition to be treated. Treatment of a large patient population through a treatment IND or treatment protocol[2] generally would require more evidence of safety and effectiveness than treatment of just a few patients. The evidence required to support expanded access for an intermediate-size patient population would be somewhere between that needed for expanded access for an individual patient and that needed for a treatment IND or treatment protocol.

In addition, as the seriousness of the disease increases, it may be appropriate to authorize expanded access use based on less data, still taking the size of the population into account. For example, to support expanded access for an individual patient when the patient has an immediately life-threatening condition that is not responsive to available therapy, ordinarily, completed phase 1 safety testing in humans at doses similar to those to be used in the treatment use, together with preliminary evidence suggesting possible effectiveness, would be sufficient to support such a use. In some cases, however, there may be no relevant clinical experience, and the case for the potential benefit may be based on preclinical data or on the mechanism of action.

In contrast, much more safety and effectiveness data would be needed to support a treatment IND or treatment protocol that anticipated enrollment of several thousand patients with a serious, but not imminently life-threatening, condition. Ordinarily, evidence of safety and effectiveness from phase 3 clinical trials would be needed to support such an expanded access use in these significantly larger populations. If the disease being treated under a treatment IND or treatment protocol were immediately life-threatening, however, compelling data from phase 2 trials might be sufficient to permit expanded access use.

2. Submission Requirements for All Expanded Access Uses

Proposed § 312.305(b)(1) states that an expanded access submission is required

[2]This proposed rule continues to describe the specific type of expanded access for treatment use that makes investigational drugs available to large populations as the "treatment IND" or "treatment protocol." We recognize that it may be confusing to carry over this terminology from our current regulations (§§ 312.34 and 312.35). However, this terminology has been used since 1987, and we believe it would be more confusing to change terminology when the nature of this type of treatment use remains essentially unchanged. The broader term "expanded access" refers to all kinds of treatment use. We solicit comment on this approach.

for each type of expanded access use. The submission may be a new IND or a protocol amendment to an existing IND. Information required for a submission may be supplied by referring to pertinent information contained in an existing IND if the sponsor of the existing IND grants a right of reference to the IND.

Proposed § 312.305(b)(2) describes the expanded access submission requirements. The following items must be included:

- A cover sheet (Form FDA 1571) meeting the requirements of § 312.23(a);
- The rationale for the intended use of the drug, including a list of available therapeutic options that would ordinarily be tried before resorting to the investigational drug or an explanation of why the use of the investigational drug is preferable to the use of available therapeutic options;
- The criteria for patient selection or, for an individual patient, a description of the patient's disease or condition, including recent medical history and previous treatments of the disease or condition;
- The method of administration of the drug, dose, and duration of therapy;
- A description of the facility where the drug will be manufactured;
- Chemistry, manufacturing, and controls information adequate to ensure the proper identification, quality, purity, and strength of the investigational drug;
- Pharmacology and toxicology information adequate to conclude that the drug is reasonably safe at the dose and duration proposed for treatment use (ordinarily, information that would be adequate to permit clinical testing of the drug in a population of the size expected to be treated); and
- A description of clinical procedures, laboratory tests, or other monitoring necessary to evaluate the effects of the drug and minimize its risks.

If this proposed rule becomes final, FDA will make educational programs and materials available to help physicians and sponsors understand the expanded access use submission requirements in general, as well as the additional information necessary to justify the different types of expanded access.

Proposed § 312.300(b)(3) requires the expanded access submission and its mailing cover to be plainly marked "EXPANDED ACCESS SUBMISSION." If the expanded access submission is for a treatment IND or treatment protocol, the applicable box on Form FDA 1571 must be checked.

3. Safeguards for All Expanded Access Uses

Proposed § 312.305(c) explains how the responsibilities of sponsors and investigators set forth in subpart D of part 312 apply to expanded access.

Proposed § 312.305(c)(1) states that a licensed physician under whose immediate direction an investigational drug is administered or dispensed for expanded access use under subpart I is considered an *investigator* for purposes of part 312 and must comply with the responsibilities for investigators set forth in subpart D of part 312 to the extent they are applicable to the expanded access use. A nonexclusive list of duties of investigators—those duties that apply in all types of expanded access—is set forth in proposed § 312.305(c)(4), and is explained further in the following paragraphs.

Proposed § 312.305(c)(2) provides that an individual or entity that submits an IND or protocol for expanded access under subpart I is considered a *sponsor* for purposes of part 312 and must comply with the responsibilities for sponsors set forth in subpart D of part 312 to the extent they are applicable to the expanded access use.

Proposed § 312.305(c)(3) provides that a licensed physician under whose immediate direction an investigational drug is administered or dispensed, and who submits an IND for expanded access under subpart I, is considered a sponsor-investigator for purposes of part 312 and must comply with the responsibilities for sponsors and investigators set forth in subpart D of part 312 to the extent they are applicable to the expanded access use.

Proposed § 312.305(c)(4) provides that, in all types of expanded access, investigators have the following responsibilities:

- Reporting adverse drug experiences to the sponsor,
- Ensuring that the informed consent requirements of 21 CFR part 50 are met,
- Ensuring that Institutional Review Board (IRB) review of the expanded access use is obtained in a manner consistent with the requirements of part 56 (21 CFR part 56), and
- Maintaining accurate case histories and drug disposition records and retaining records in a manner consistent with the requirements of § 312.62.

However, this list of duties under subpart D of part 312 is not exclusive, and other requirements may apply, depending on the particular type of expanded access.

Proposed § 312.305(c)(5) provides that, in all cases, sponsors have the following responsibilities:

- Submitting IND safety reports and annual reports (when the IND or protocol continues for 1 year or longer) to FDA as required by §§ 312.32 and 312.33,
- Ensuring that licensed physicians are qualified to administer the investigational drug for the expanded access use,
- Providing licensed physicians with the information needed to minimize the risk and maximize the potential benefits of the investigational drug (e.g., providing the investigator's brochure, if there is one),
- Maintaining an effective IND for the expanded access use, and
- Maintaining adequate drug disposition records and retaining records in a manner consistent with the requirements of § 312.57.

As with the list of investigator's duties under proposed § 312.305(c)(4), this list of sponsor's duties under subpart D of part 312 is not exclusive, and other requirements may apply, depending on the particular type of expanded access.

4. When Expanded Access Use May Begin

Proposed § 312.305(d) explains when expanded access use may begin, assuming FDA has not placed a clinical hold on the expanded access use. Under IND rules, a study described in a protocol in a newly submitted IND can begin 30 days after FDA receipt of the IND (or on earlier notification by FDA that the study may proceed), unless FDA puts the study on hold. Once there is an IND in place, new protocols submitted to that IND may begin on the date of submission.

Proposed § 312.300(d)(1) states that an expanded access IND goes into effect 30 days after FDA receives the IND or on earlier notification by FDA that the expanded access use may begin, consistent with FDA's normal practice.

Proposed § 312.300(d)(2) explains when expanded access use may begin, if the expanded access submission is in the form of a new protocol submitted under an existing IND. The proposed rule states that expanded access use under a protocol submitted under an existing IND may begin as described in § 312.30(a). Section 312.30(a) provides that the study under the protocol may begin provided two conditions are met: (1) The sponsor has submitted the protocol to FDA for its review and (2) the protocol has been approved by the IRB with responsibility for review and approval of the study in accordance with the requirements of part 56. Section 312.30(a) states that the sponsor may comply with these two conditions in either order.

The proposed rule provides two exceptions to the general rules concerning when expanded access use under a new protocol may begin. First, proposed § 312.305(d)(2)(i) provides that treatment under a protocol for individual patient expanded access in an emergency situation may begin when it is authorized by the FDA reviewing official. Second, proposed § 312.305(d)(2)(ii) states that expanded access use under proposed § 312.320 (the treatment IND or treatment protocol described in §§ 312.34 and 312.35 of the current IND regulations) may begin 30 days after FDA receives the protocol (or on earlier notification by FDA that the treatment use may begin); that is, there would be a 30-day wait even for a protocol submitted under an existing IND. Expanded access use under a treatment IND or treatment protocol often involves thousands of patients. The agency believes it is important to build in time for agency review of a proposed expanded access use with the potential to affect so many people.

Proposed § 312.300(d)(3) states that FDA may place any expanded access IND or protocol on clinical hold as described in § 312.42.

*F. Expanded Access for Individual Patients (Proposed § 312.310)*

Proposed § 312.310 would permit an investigational drug to be used for the treatment of an individual patient by a licensed physician.

1. Expanded Access for Individual Patients—Criteria

In addition to the proposed criteria for all expanded access uses, proposed § 312.310(a) sets forth two criteria for permitting an investigational drug to be used for the treatment of an individual patient by a licensed physician.

- First, the physician must determine that the probable risk to the person from the investigational drug is not greater than the probable risk from the disease or condition (proposed § 312.310(a)(1)).
- Second, FDA must determine that the patient cannot obtain the drug under another type of IND (proposed § 312.310(a)(2)). (Section 561(b)(3) of the act requires that FDA determine that provision of the investigational drug will not interfere with the initiation, conduct, or completion of clinical investigations to support marketing approval.) Thus, expanded access for an individual patient would not be available, for example, if the patient can participate in a clinical trial of the investigational drug. However, participation in a clinical trial may not be possible for many reasons. A patient may have a stage of the disease different from the stage being studied. The patient may have failed on, or be intolerant of, the active control in a randomized active-control trial. It may be geographically impossible for the patient to participate in a clinical trial.

One of the proposed general criteria for any expanded access use is that FDA must determine that the potential benefit to the patient justifies the potential risks of the expanded access use and those potential risks are not unreasonable in the context of the disease or condition to be treated. The evidence needed to make this determination for expanded access for an individual patient will vary. For a patient with an immediately life-threatening condition, the evidentiary burden could be very low—little if any clinical evidence to suggest a potential benefit or possibly only animal data to support safety of the use. For a patient with a serious, but not immediately life-threatening, condition who could expect to enjoy a reasonable quality of life for an extended time without any treatment, the evidentiary burden would be higher.

2. Expanded Access for Individual Patients—Submission Requirements

In addition to the proposed submission requirements for all expanded access uses, proposed § 312.310(b) provides that the expanded access submission must include information adequate to demonstrate that the general criteria for expanded access use and those specific to expanded access for individual patients have been met.

Proposed § 312.310(b) provides that if the drug is the subject of an existing IND, the expanded access submission may be made by the sponsor or by a licensed physician. A sponsor may satisfy the submission requirements by amending its existing IND to include a protocol for individual patient expanded access. Sponsors are strongly encouraged to include individual patient expanded access protocols under their own INDs.

Proposed § 312.310(b) provides that a licensed physician may satisfy the submission requirements by obtaining from the sponsor permission for FDA to refer to any information in the IND that would be needed to support the individual patient expanded access request (right of reference) and by providing any other required information not contained in the IND (usually only the information specific to the individual patient). Obtaining a right of reference is consistent with current practice. Sponsors who agree to make an investigational drug available to an individual patient, but prefer that it be provided under an IND obtained by the licensed physician rather than under the sponsor's IND, routinely provide a right of reference to necessary information in the existing IND, and such a right of reference is necessary for FDA to be able to make the necessary determinations about whether the expanded access use may proceed.

3. Expanded Access for Individual Patients—Safeguards

Proposed § 312.310(c) sets forth safeguards that apply specifically to expanded access for individual patients. These proposed safeguards are listed as follows:

- Treatment of an individual patient with an investigational drug is generally limited to a single course of therapy for a specified duration, unless FDA expressly authorizes multiple courses or chronic therapy.
- FDA may require sponsors to monitor an individual patient expanded access use if the use is for an extended duration.
- At the conclusion of treatment, the licensed physician or sponsor (whoever made the expanded access submission) must provide a written summary of the results of the treatment use, including unexpected adverse drug experiences.
- When FDA receives a significant number of similar requests for individual patient expanded access, the agency may ask the sponsor to submit an IND or protocol for the use under § 312.315 or § 312.320.

What constitutes a significant number of similar requests will vary depending on the indication, the number of patients with no available therapeutic options, and the extent to which the drug has the potential to benefit those patients. In general, when the agency receives 10 or more requests for the same individual patient expanded access use within a relatively short time period (e.g., less than 6 months), FDA will consider whether to request that a potential sponsor submit an intermediate-size patient population IND or protocol for the expanded access use and, possibly, conduct a clinical trial of the expanded access use.

4. Expanded Access for Individual Patients—Emergency Procedures

Proposed § 312.310(d) sets out emergency procedures for expanded access for individual patients. If there is an emergency that requires a patient to be treated before a written submission can be made, FDA may authorize the expanded access use to begin without a written submission. Under the proposed rule, the FDA reviewing official may

authorize the emergency use by telephone. Emergency expanded access use may be requested by telephone, facsimile, or other means of electronic communications. The proposed rule also provides phone numbers for requests for investigational drugs and investigational biological drug products, and an after-hours contact number.

Proposed § 312.310(d)(2) requires the licensed physician or sponsor to explain how the expanded access use will meet the requirements of proposed §§ 312.305 and 312.310 and requires agreement to submit an expanded access submission that complies with proposed §§ 312.305 and 312.310 within 5 working days of FDA's authorization of the expanded access use.

For individual patient expanded access use situations in which there is time to make a written submission, the expedited procedures would not be available. Lack of a prior written submission decreases FDA's ability to review the proposed use. Furthermore, FDA's experience with emergency treatment use is that the written submission and followup information on the outcome of the treatment use frequently have not been provided. By limiting use of the emergency procedures to true emergencies, the agency hopes to better monitor individual patient expanded access use.

*G. Expanded Access for Intermediate-Size Patient Populations (Proposed § 312.315)*

Proposed § 312.315 provides for expanded access use by patient populations smaller than those typical in treatment INDs or treatment protocols. FDA may ask a sponsor to consolidate expanded access use under this section when the agency has received a significant number of requests for individual patient expanded access to an investigational drug for the same use.

Proposed § 312.315(a) states that expanded access use under the section may be needed in the following situations:

- Drug not being developed. The drug is not being developed, for example, because the disease or condition is so rare that the sponsor is unable to recruit patients for a clinical trial. Nonetheless, the drug may represent the only promising therapy for the people with the disease or condition (proposed § 312.315(a)(1)).
- Drug being developed. The drug is being studied in a clinical trial, but patients requesting the drug for expanded access use are unable to participate in the trial. Patients may not be able to participate in the trial, for example, because they have a different disease or stage of disease from the one being studied or otherwise do not meet the enrollment criteria; because enrollment in the trial is closed; or because the trial site is not geographically accessible (proposed § 312.315(a)(2)).
- Approved or related drug. The drug is an approved drug product that is no longer marketed for safety reasons or is unavailable through marketing due to failure to meet the conditions of the approved application (proposed § 312.315(a)(3)(i)), or the drug contains the same active moiety as an approved drug product that is unavailable through marketing due to failure to meet the conditions of the approved application or a drug shortage (proposed § 312.315(a)(3)(ii)).

When a drug is no longer marketed due to safety reasons, there may be a subset of patients for whom the benefits of treatment are believed to outweigh the risks and who lack satisfactory alternative therapies. Under proposed § 312.315(a)(3)(i), those patients could continue to receive the drug under an intermediate-size patient population IND for expanded access use.

This provision is also intended to allow uninterrupted therapy when an approved drug is not being manufactured in a manner consistent with the specifications on which the approval is based (good manufacturing practice (GMP) violations) and therefore cannot be marketed under the new drug application (NDA). Under proposed § 312.315(a)(3)(i), the drug could be made available to patients for whom the drug is a medical necessity until the GMP violations are addressed (assuming that, despite those violations, the product does not pose a risk that is unreasonable in the context of the disease or condition to be treated, per proposed § 312.305(a)(2)). If the product does pose a risk because of GMP concerns, proposed § 312.315(a)(3)(ii) could be used to make available an unapproved drug product containing the same active moiety (e.g., a drug product approved in another country).

Proposed § 312.315(a)(3)(ii) could also be used in a drug shortage situation to make available an unapproved drug containing the same active moiety as the approved drug that is in short supply (e.g., a drug product approved in another country).

1. Expanded Access for Intermediate-Size Patient Populations—Criteria

In addition to the proposed criteria for all expanded access uses, proposed § 312.315(b) sets forth the criteria that apply specifically to expanded access use for intermediate-size patient populations.

- The first criterion requires that there be enough evidence that the drug is safe at the dose and duration proposed for expanded access use to justify a clinical trial of the drug in the approximate number of patients expected to receive the drug for expanded access use (proposed § 312.315(b)(1)).

In ordinary drug development, it is usual practice to gradually increase the number of subjects exposed to a drug (from first human exposure in a very small number of subjects through large phase 3 trials). This practice limits the risk from drugs that turn out to have significant adverse effects, as more and better information (e.g., about dosing) is obtained about the drug before larger numbers of subjects are treated. The same rationale would apply in the expanded access use setting. There should be more clinical experience for an intermediate-size patient population than for an individual patient, and the amount of clinical experience to justify expanded access use in a certain population should be roughly the same as would justify a clinical trial in that size population. FDA anticipates that the typical intermediate-size patient population treatment use IND or protocol will provide access to between 10 and 100 patients.

- The second criterion requires that there be at least preliminary clinical evidence of effectiveness of the drug or of a plausible pharmacologic effect of the drug to make expanded access use a reasonable therapeutic option in the anticipated patient population (proposed § 312.315(b)(2)).

2. Expanded Access for Intermediate-Size Patient Populations—Submission Requirements

In addition to the proposed submission requirements for all expanded access uses, proposed § 312.315(c) sets forth the submission requirements that apply specifically to expanded access use by intermediate-size patient populations. The expanded access use submission must do the following:

- State whether the drug is being developed or is not being developed and describe the patient population to be treated (proposed § 312.315(c)(1));
- Include an explanation by the sponsor, if the drug is not being actively developed, of why the drug cannot currently be developed for the expanded access use and under what circumstances the drug could be developed (proposed § 312.315(c)(2)); and

• Include an explanation by the sponsor, if the drug is being studied in a clinical trial, of why the patients to be treated cannot be enrolled in the clinical trial and under what circumstances the sponsor would conduct a clinical trial in these patients (proposed § 312.315(c)(3)).

3. Expanded Access for Intermediate-Size Patient Populations—Safeguards

Proposed § 312.315(d) sets forth the safeguards that apply specifically to expanded access use by intermediate-size populations. Upon review of the IND annual report, FDA will determine whether it is appropriate for the use to continue under this section. If the drug is not being actively developed or if the expanded access use is not being developed (but another use is being developed), FDA will consider whether it is possible to conduct a clinical study to develop the expanded access use for marketing (proposed § 312.315(d)(1)(i)). If the drug is being actively developed, FDA will consider whether providing the investigational drug for expanded access use is interfering with the clinical development of the drug (proposed § 312.315(d)(1)(ii)). As the number of patients enrolled increases, FDA will also consider whether to request that a sponsor submit a treatment IND or treatment protocol as described in § 312.320 for the expanded access use (proposed § 312.315(d)(1)(iii)). The sponsor is responsible for monitoring the expanded access protocol to ensure that licensed physicians comply with the protocol and the regulations applicable to investigators (proposed § 312.315(d)(2)).

*H. Expanded Access Treatment IND or Treatment Protocol (Proposed § 312.320)*

Proposed § 312.320 describes the treatment IND or treatment protocol mechanism that is currently provided in §§ 312.34 and 312.35. Proposed § 312.320 retains the basic terminology "treatment IND" and "treatment protocol" from current §§ 312.34 and 312.35.

1. Expanded Access Treatment IND or Treatment Protocol—Criteria

In addition to the proposed criteria for all expanded access uses, proposed § 312.320(a) provides the criteria that apply specifically to a treatment IND or treatment protocol.

Proposed § 312.320(a)(1) requires that either the drug is being investigated in a controlled clinical trial under an IND designed to support a marketing application for the expanded access use (proposed § 312.320(a)(1)(i)), or all clinical trials of the drug have been completed (proposed § 312.320(a)(1)(ii)).

In addition, the sponsor must be actively pursuing marketing approval of the drug for the expanded access use with due diligence (proposed § 312.320(a)(2)).

Proposed § 312.320(a)(3)(i) provides that, when the expanded access use is for a serious disease or condition, there must be sufficient clinical evidence of safety and effectiveness to support the expanded access use. Such evidence would ordinarily consist of data from phase 3 trials, but could consist of compelling data from completed phase 2 trials.

Proposed § 312.320(a)(2)(ii) provides that, when the expanded access use is for an immediately life-threatening disease or condition, the available scientific evidence, taken as a whole, provides a reasonable basis to conclude that the investigational drug may be effective for the expanded access use and would not expose patients to an unreasonable and significant risk of illness or injury. This evidence would ordinarily consist of clinical data from phase 3 or phase 2 trials, but could be based on more preliminary clinical evidence.

2. Expanded Access Treatment IND or Treatment Protocol—Submission Requirements

In addition to the proposed submission requirements for all expanded access uses, proposed § 312.320(b) states that the expanded access submission must include information adequate to satisfy FDA that the general criteria for expanded access use and those specific to the treatment IND or treatment protocol have been met.

3. Expanded Access Treatment IND or Treatment Protocol—Safeguards

Proposed § 312.320(c) provides a safeguard that applies specifically to treatment protocols. The sponsor is responsible for monitoring the treatment protocol to ensure that licensed physicians comply with the protocol and the regulations applicable to investigators.

*I. Open-Label Safety Studies*

The primary purpose of the treatment IND or treatment protocol is to make investigational drugs available to patients with serious or immediately life-threatening diseases or conditions when there is a reasonable evidentiary basis to support the use in a substantial population, but the evidence needed for marketing approval either has not been entirely collected or has been collected but not yet analyzed and reviewed by the agency.

FDA is concerned that sponsors have used programs other than treatment INDs or treatment protocols to make investigational drugs available to large populations for treatment use, particularly by identifying such programs as "open-label safety studies." The goal of an open-label safety study is to better characterize the safety of a drug late in its development. However, in practice, many studies that are described as open-label safety studies have characteristics that appear to be more consistent with treatment INDs or treatment protocols. For example:

• The investigators are not selected by the sponsor but can be any physician (sometimes with specified qualifications),

• The population receiving the drug is quite large,

• Collection of data is minimal, and

• The studies may not generate the kind of reliable information that would be developed in a study designed to meaningfully assess safety endpoints.

Consequently, in the future, the agency intends to evaluate whether proposals for open-label safety studies should be treatment INDs or treatment protocols that would have to meet the criteria in proposed § 312.320. A study described as an open-label safety study that provides broad access to an investigational drug in the later stages of development, but lacks planned, systematic data collection and a design appropriate to evaluation of a safety issue is likely to be considered a treatment IND or treatment protocol. The agency believes treatment INDs or treatment protocols are more appropriate programs to provide treatment because the authorization for such expanded access uses will require a more formal review process that would explicitly consider the impact of expanded access on enrollment in clinical trials and the progress of drug development generally.

*J. Continuation Phase of a Clinical Trial*

The continuation phase of a clinical trial may have characteristics in common with open-label safety studies or expanded access, or both. In the continuation phase of a clinical trial, patients have the option of receiving the study drug after completing the controlled portion of the trial (continue on the study drug or cross over from a control treatment to the study drug), often as an inducement to enroll in the clinical study. All patients receive the study drug. The primary intent may be to develop additional safety data or to

treat the patient's condition. Notwithstanding the intent, however, because enrollment is limited to only clinical study participants, the use is considered a part of the clinical study rather than an expanded access use for purposes of proposed subpart I.

## V. Legal Authority

The agency believes it has the authority to impose requirements regarding expanded access to investigational drugs under various sections of the act, including sections 505(i); 561; and 701(a) (21 U.S.C. 371(a)).

Section 505(i) of the act directs the agency[3] to issue regulations exempting from the operation of the new drug approval requirements drugs intended solely for investigational use by experts qualified by scientific training and expertise to investigate the safety and effectiveness of drugs. The proposed rule explains procedures for obtaining FDA authorization for expanded access uses of investigational drugs and factors relevant to making necessary determinations.

Section 561 of the act, added by FDAMA, provides significant additional authority for this proposed rule. Section 561(a) of the act states that FDA may, under appropriate conditions determined by the agency, authorize the shipment of investigational drugs for the diagnosis, monitoring, or treatment of a serious disease or condition in emergency situations. This proposed rule sets forth factors that the agency will consider in determining whether to authorize shipment of investigational drugs in emergency situations.

Section 561(b) of the act allows any person, acting through a physician licensed in accordance with State law, to request from a manufacturer or distributor an investigational drug for the diagnosis, monitoring, or treatment of a serious disease or condition if four conditions are met: (1) The physician must determine that the person has no comparable or satisfactory alternative therapy available and the probable risk to the person from the investigational drug is not greater than the probable risk from the disease or condition; (2) FDA must determine that there is sufficient evidence of safety and effectiveness to support the use of the investigational drug in the particular case; (3) FDA must determine that provision of the investigational drug will not interfere with the initiation, conduct, or completion of clinical investigations to support marketing approval; and (4) the sponsor or clinical investigator of the investigational drug submits a clinical protocol consistent with the provisions of section 505 of the act describing the use of the investigational drug in a single patient or a small group of patients. The proposed rule sets forth factors that FDA will consider in making the necessary determinations and explains the procedures and criteria for physicians, sponsors, and/or investigators to make the necessary representations and submissions to FDA.

Section 561(c) of the act specifically authorizes expanded access under a treatment IND if FDA makes the following determinations: (1) Under the treatment IND, the investigational drug is intended for use in diagnosing, monitoring, or treating a serious or immediately life-threatening disease or condition; (2) there is no comparable or satisfactory alternative therapy available to diagnose, monitor, or treat that stage of disease or condition in the population of patients to which the investigational drug is intended to be administered; (3) the investigational drug is already under investigation in a controlled clinical trial for the same use under an IND under section 505(i) of the act, or all clinical trials necessary for approval of that use of the investigational drug have been completed; (4) the sponsor of the controlled clinical trials is actively pursuing marketing approval of the investigational drug, with due diligence, for the same intended use; (5) provision of the investigational drug will not interfere with the enrollment of patients in ongoing clinical investigations under section 505(i) of the act; (6) in the case of serious diseases, there is sufficient evidence of safety and effectiveness to support the intended use; and (7) in the case of immediately life-threatening diseases, the available scientific evidence, taken as a whole, provides a reasonable basis to conclude that the investigational drug may be effective for its intended use and would not expose patients to an unreasonable and significant risk of illness and injury. The proposed rule sets forth factors that FDA will consider in making the necessary determinations.

Section 561 of the act further requires that protocols submitted under section 561 be subject to section 505(i) of the act including regulations issued under section 505(i). Section 561(d) of the act permits the agency to terminate expanded access for failure to comply with the requirements of section 561 of the act. The proposed rule sets forth the conditions under which FDA will place an expanded access use on clinical hold.

In this proposed rule, the agency proposes three categories of expanded access. While authority for individual patient access is based on section 561(b) of the act, and authority for treatment INDs and treatment protocols is based on section 561(c) of the act, there is also authority in the statute for FDA to issue regulations for intermediate-size patient populations. Section 561(b)(4) of the act requires submission of a protocol for the expanded access use that is consistent with the requirements of the IND regulations describing the use of the investigational drug in a single patient or a small group of patients. The provisions of the proposed rule concerning expanded access for intermediate-size patient populations address the use of the investigational drug in the small groups of patients mentioned in the statute.

Section 701(a) of the act provides general authority to issue regulations for the efficient enforcement of the act. By clarifying the criteria and procedures relating to expanded access to investigational products, this proposed rule is expected to aid in the efficient enforcement of the act.

## VI. Environmental Impact

The agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

## VII. Analysis of Economic Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and under the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this proposed rule is not an economically significant regulatory action as defined by the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small

[3] In light of section 903(d) of the act (21 U.S.C. 393(d)) and the Secretary's delegations to the Commissioner of Food and Drugs, statutory references to "the Secretary" in the discussion of legal authority have been changed to "FDA" or "the agency."

entities. Currently, the agency does not believe that the proposed rule will have a significant economic impact on a substantial number of small entities. Nevertheless, we recognize our uncertainty regarding the number and size distribution of affected entities, as well as the economic impact of the proposed rule on those entities. Therefore, this economic analysis, together with other relevant sections of this document, constitutes the agency's initial regulatory flexibility analysis. The agency specifically requests detailed public comment regarding the number of affected small entities as well as the potential economic impact of the proposed rule on those entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in an expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is approximately $122 million, using the most current (2005) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this proposed rule to result in any 1-year expenditure that would meet or exceed this amount.

*A. Objectives of the Proposed Action*

FDA is proposing this action to describe in greater detail all of the ways patients may obtain expanded access to investigational drugs for treatment use. Specifically, the proposed rule establishes eligibility criteria, submission requirements, and safeguards for the expanded access use of investigational drugs by individual patients, including in emergencies; intermediate size patient populations; and larger populations under a treatment protocol or treatment IND. The proposal is also intended to increase public knowledge and awareness of expanded access and, thus, to make investigational drugs more widely available. In addition, by establishing clear eligibility criteria and submission requirements, the proposed rule would ease administrative burdens on physicians seeking investigational drugs for their patients and on sponsors who are willing to make promising unapproved therapies available for treatment use. The agency believes that the proposed rule would achieve these objectives in a way that fairly addresses the interests of patients, drug sponsors, and society as a whole.

*B. Nature of the Problem Being Addressed*

The fundamental problem addressed by the proposed rule is one of incomplete information. In some circumstances, a lack of clearly defined eligibility criteria and submission requirements has created inefficiencies that limit patient access to potentially beneficial investigational drugs. The proposed rule is also intended to address concerns that, historically, cancer and AIDS patients have had better access to investigational drugs than patients with other serious diseases or conditions, and that patients under the care of physicians based in academic medical centers are more likely to obtain such access than patients whose physicians practice outside such centers. In addition, the lack of clearly defined eligibility criteria and submission requirements has led some physicians and drug sponsors to devote more resources than necessary to the preparation of expanded access submissions. Through this proposed rule, the agency seeks to correct these shortcomings.

The proposed rule establishes general eligibility criteria, submission requirements, and safeguards for the expanded access use of investigational drugs. The requirements that apply to all types of expanded access use are described in detail in section IV.E of this document. The proposed rule also describes more specific eligibility criteria, submission requirements, and safeguards for three specific categories of expanded access: (1) Expanded access for individual patients, (2) expanded access for intermediate-size patient populations, and (3) expanded access under a treatment protocol or treatment IND. These types of expanded access uses are described in detail in sections IV.F, IV.G, and IV.H of this document, respectively.

*C. Baseline for the Analysis*

During the period 1997 through 2005, FDA received an average of 2,046.6 INDs per year. Of this number, on average, approximately 659, or 32.2 percent (0.322 = 659 / 2,046.6) were individual patient or emergency INDs. In addition, FDA received approximately 4.6 treatment IND or treatment protocol submissions per year during this time period. Thus, treatment IND or treatment protocol submissions represent about 0.2 percent (0.022 = 4.6 / 2,046.6) of all INDs received by the agency each year. Because expanded access for intermediate size patient populations is not currently established in regulation, FDA does not have a record of the number of submissions in this category. However, based on an internal survey of drug review divisions, FDA estimates that approximately 55 other expanded access submissions were received each year between 2000 and 2002. While it is not possible to determine the precise number that would be considered intermediate size patient population expanded access submissions, FDA experts believe that most of the 55 other submissions each year would fall under this category. Thus, approximately 2.7 percent (0.0268 = 55 / 2,046.6) of all INDs received by FDA each year may be associated with intermediate size patient population expanded access requests. The information presented above is summarized in table 1 of this document.

TABLE 1.—BASELINE DATA FOR THE NUMBER OF INDS AND EXPANDED ACCESS REQUESTS BY CATEGORY

| Category | Total INDs | Individual Patient or Emergency IND | Treatment IND or Protocol | Other |
|---|---|---|---|---|
| Number | 2,046.6 | 659.0 | 4.6 | 55.0 |
| Percent of all INDs | 100% | 32.2% | 0.2% | 2.7% |

*D. Nature of the Impact*

The proposed rule would affect patients who lack effective therapeutic alternatives and may benefit from access to investigational drugs, physicians attempting to obtain investigational drugs for their patients, drug sponsors who make investigational drugs available to patients, and FDA in its oversight role in the process for making investigational drugs available for expanded access use. As discussed

further in section I.D of this document, a major purpose of this proposed rule is to expand access to investigational drugs for patients with serious and immediately life-threatening conditions who lack satisfactory therapeutic alternatives. Therefore, FDA anticipates that the proposed rule would increase the number of patients who obtain access to investigational drugs for treatment use. This increase in volume would lead to more expanded access submissions from sponsors and physicians seeking investigational drugs for their patients and, as a consequence, would require FDA to review more submissions. Given the relatively small percentage of all INDs received by the agency that are associated with expanded access use submissions, FDA expects that the overall impact of the proposed rule will not be significant.

The proposed rule also attempts to minimize the potential administrative burdens for physicians, sponsors, and FDA that would result from an increased volume of patients obtaining investigational drugs for expanded access use. The proposed rule encourages the consolidation of multiple individual patient INDs or protocols for a given use under an intermediate-size patient population IND or protocol (see sections VII.D.2 and VII.F of this document for additional discussion). By reducing the total volume of submissions that would have been prepared if all patients were to obtain a drug under individual patient INDs or protocols, consolidation will limit the additional administrative burdens from increased patient access. In addition, by explicitly clarifying the eligibility criteria and submission requirements for expanded access, the proposed rule should make the process of obtaining access to investigational drugs more efficient for all affected parties.

It is expected that any increase in the volume of submissions would result primarily from greater numbers of patients obtaining investigational drugs under expanded access INDs or protocols for individual patients and intermediate-size patient populations. Because this proposed rule does not significantly change the existing regulation concerning treatment INDs or treatment protocols, the number of patients receiving investigational drugs under these mechanisms should be largely unaffected.

1. Individual Patient Expanded Access Submissions

By increasing awareness of the ways individual patients can obtain expanded access to investigational drugs for treatment use, and decreasing the perceived difficulty of obtaining such access, the proposed rule should increase the number of individual patients seeking access to investigational drugs. FDA anticipates that this increase in individual patient expanded access submissions would be greatest in the years immediately following implementation of a final rule and would at some point level off, or possibly even decline. This leveling off or decline would occur when a significant volume of individual patient expanded access has accumulated for a variety of drugs, and the individual patient expanded access INDs or protocols for those drugs are then replaced with intermediate-size patient population INDs or protocols that enroll multiple subjects. Making the transition from multiple individual patient INDs or protocols to a single intermediate-size patient population IND or protocol should reduce the overall administrative burden associated with making a particular investigational drug available for treatment use.

From 1997 to 2005, FDA received, on average, approximately 659 individual patient and emergency IND submissions per year. Although FDA is confident this proposed rule would increase this volume, it is difficult to predict with precision the extent of the increase. There is uncertainty concerning the extent to which patients who desire expanded access to investigational drugs are unable to obtain them; the extent to which better information about the mechanisms and processes for obtaining access to investigational drugs will stimulate more patients, or their physicians, to seek investigational drugs for expanded access use; and the extent to which drug manufacturers will be willing to make investigational drugs more broadly available for expanded access use. Although FDA is confident there will be an increase in the volume of individual patient expanded access use if this rulemaking is finalized, because of these uncertainties the agency can provide only an estimate of the range of potential increase. FDA believes, after publication of a final rule, that it is reasonable to anticipate a 40 to 60 percent increase in the volume of individual patient expanded access submissions by year 3. As discussed previously in this document, we anticipate that growth would be most rapid in the years immediately following publication of a final rule and would eventually plateau, or possibly even decline. The implications of these assumptions for the total number of individual patient expanded access submissions are summarized in table 2 of this document.

TABLE 2.—EXPECTED PERCENT INCREASE AND ESTIMATED NUMBER OF INDIVIDUAL PATIENT EXPANDED ACCESS SUBMISSIONS

| Year After Implementation of Final Rule | Expected Percent Increase in Individual Patient Submissions | Expected Number of Individual Patient Submissions[1] |
|---|---|---|
| 1 | 20% to 40% | 791 to 923 |
| 2 | 30% to 50% | 857 to 988 |
| 3 | 40% to 60% | 923 to 1,054 |
| 4 | 0% | 923 to 1,054 |
| 5 | 0% | 923 to 1,054 |

[1]Based on the current average of 659 individual patient treatment use submissions per year and the estimated percent increases in column 2.

2. Intermediate Size Patient Population Expanded Access Submissions

Although intermediate-size patient population expanded access has not previously been described in regulation, this general type of mechanism has been used informally to make investigational drugs available for treatment use. Based on an internal survey of review divisions, FDA estimates that for the period 2000 through 2002 it received approximately 55 submissions per year that would be considered intermediate size patient population expanded access submissions under the proposed criteria. The agency anticipates that this proposed rule would increase the number of such submissions. Because this previously informal mechanism will be described in regulation for the first time, there will be greater awareness, which is likely to stimulate submissions. In addition, the anticipated increase in volume of individual patient expanded access submissions discussed previously in this document is expected to increase the number of intermediate size patient population expanded access submissions because the proposed rule encourages the consolidation of multiple individual patient INDs or protocols for a given expanded access use.

The extent to which submissions for expanded access for intermediate-size patient populations will increase is uncertain. Section 312.315 of the proposed rule concerns expanded access for intermediate-size patient populations. This section provides that

FDA may ask a sponsor to consolidate expanded access under this section when the agency has received a significant number of requests for individual patient expanded access to an investigational drug for the same use. FDA does not have historical information that would permit us to accurately predict what portion of individual patient expanded access submissions are likely to be appropriate for consolidation. Based on our experience, we believe that many of the individual patient expanded access submissions we receive will be appropriate for consolidation. However, some individual patient expanded access submissions will be for expanded access uses that are sufficiently rare that it is unlikely that there will be enough similar uses to consolidate them under an intermediate-size patient population IND or protocol. There is also uncertainty about the extent to which sponsors will be willing to make investigational drugs available for expanded access use under intermediate-size patient population INDs or protocols. Although FDA is confident that there will be growth in the volume of intermediate-size patient population expanded access INDs or protocols, because of the uncertainties identified, we can provide only an estimate of the range of potential increase. FDA believes it is reasonable to anticipate a 25 to 50 percent growth in the volume of submissions for intermediate-size population expanded access INDs or protocols over a 5-year period.

Compared to the growth in individual patient expanded access submissions, this increase is likely to be more gradual in the years immediately following implementation of a final rule, and will increase more sharply after 2 to 3 years as some of the increase in volume of individual patient expanded access submissions is shifted to intermediate size population INDs or protocols. As in the case of expanded access for individual patients, growth in the number of submissions is expected to plateau or even decline after a few years. The implications of these assumptions for the number of individual patient expanded access submissions are summarized in table 3 of this document.

TABLE 3.—EXPECTED PERCENT INCREASE AND ESTIMATED NUMBER OF INTERMEDIATE SIZE PATIENT POPULATION EXPANDED ACCESS SUBMISSIONS

| Year After Implementation of Final Rule | Expected Percent Increase in Intermediate Size Patient Population Submissions | Expected Number of Intermediate Size Patient Population Submissions[1] |
|---|---|---|
| 1 | 5% to 10% | 58 to 61 |
| 2 | 10% to 20% | 61 to 66 |
| 3 | 20% to 40% | 66 to 77 |
| 4 | 25% to 50% | 69 to 82 |
| 5 | 0% | 69 to 82 |

[1]Based on the current average of 55 intermediate size patient population submissions per year and the estimated percent increases in column 2.

3. Expanded Access Under Treatment INDs and Treatment Protocols

The number of treatment INDs and treatment protocols should be largely unaffected by the proposed rule. The concept of large access programs is well established and most drugs that meet an unmet medical need for a serious or immediately life-threatening condition have had some kind of large access program late in their development. Therefore, the number of large access programs is primarily a function of the number of new drugs to treat serious and immediately life-threatening conditions that reach the latter stages of drug development (e.g., become NDA submissions). This rule is unlikely to influence that number.

As discussed previously in this document, sponsors have instituted large expanded access programs under treatment INDs or treatment protocols or under less formal open-label or open-access protocols (see section IV.I of this document). The agency intends to be more vigilant in ensuring that a use of an investigational drug that has the characteristics of a treatment IND or treatment protocol is submitted and authorized as such, rather than as an open-label protocol. While this increased vigilance may increase the number of treatment INDs or treatment protocols, any increase will be primarily attributable to reclassifying open-label safety studies as treatment INDs or treatment protocols rather than a net increase in the overall number of large access programs. This reclassification should also improve safety monitoring of large access programs without significantly increasing administrative costs, because the costs for a treatment IND or treatment protocol and an open-label protocol are similar.

Reclassification of an open-label protocol as a treatment IND or treatment protocol may also increase publicity for, and awareness of, the access program. Sponsors of treatment INDs or treatment protocols are required to list those programs at *http://www.clinicaltrials.gov*, a Web site maintained by the National Institutes of Health as a resource for patients seeking to enroll in clinical trials or obtain access to investigational drugs for treatment use. The additional exposure generated by this site may attract more patients than would have had access under an open-label protocol. As a result, any given treatment IND or treatment protocol may be somewhat more costly than a less publicized open-label protocol due to the volume of patients enrolled. FDA is not able to predict the impact on patient volume as a result of reclassifying open-label or open-access protocols as treatment INDs or treatment protocols. However, FDA anticipates that there would be some economies of scale, so that the incremental costs would be relatively small on a per-patient basis. FDA believes any added costs would be justified by the potentially greater number of patients who would benefit from access to investigational drugs.

*E. Benefits of the Proposed Rule*

Because FDA currently has no data that would allow us to predict the extent to which the proposed amendments to existing IND regulations would generate direct benefits for consumers, it is not possible to accurately quantify the magnitude of any expected incremental benefits at this time. The number of patients obtaining expanded access to investigational drugs is expected to increase. However, because eligible patients will have serious or immediately life-threatening conditions that have failed to respond to available therapies, and because the investigational drugs are unproven, FDA cannot predict the extent to which individual patients would benefit from access to these drugs. Thus, the following discussion describes, in general terms, the nature of the potential benefits associated with the proposed rule.

The benefits of the proposed rule are expected to result from improved patient access to investigational drugs generally and from expanded access being made available for a broader variety of disease conditions and

treatment settings. In particular, the clarification of eligibility criteria and submission requirements would enhance patient access by easing the administrative burdens on individual physicians seeking investigational drugs for their patients and on sponsors who make investigational drugs available for expanded access use. Expanded access to investigational drugs may generate both private and social benefits. Private benefits would accrue to individual patients receiving drugs for expanded access use, whereas social benefits would accrue if these private benefits are also valued by society at large, or if any information obtained contributes to the development of new therapies generally.

The proposed rule is also designed to address concerns that many physicians and their patients, particularly those outside of academic medical centers, are unaware of the availability of investigational drugs for expanded access use. In FDAMA, Congress included language in section 561(c) of the act to authorize the Secretary to inform medical associations, medical societies, and other appropriate persons of the availability of investigational drugs under treatment INDs or treatment protocols. FDA believes that this action, along with detailed eligibility criteria and submission requirements established in the proposed rule, would improve access to investigational drugs and result in making expanded access use more widely available to patients regardless of treatment setting.

In formulating the proposed rule, FDA considered its statutory mandate, the interests of individuals and special patient populations, drug sponsors, and the general public. The agency found that in many situations, individuals or special patient populations have benefited from increased access to a drug that has not yet been approved for marketing (e.g., in the case of cancer or HIV therapies, etc.). These individuals or patient groups generally have serious or immediately life-threatening conditions and have not responded to available therapies or cannot participate in ongoing clinical trials for some reason.

On the other hand unrestricted access to investigational drugs for treatment use could negatively affect enrollment in the clinical trials required to demonstrate safety and efficacy in support of new drug marketing applications. If expanded access to investigational drugs were to adversely affect the marketing approval process, the general population would experience diminished social benefits due to the reduced or delayed availability of new therapies approved for marketing by FDA.

The proposed rule addresses these competing interests by allowing investigational drugs to be made available for expanded access use only if providing the drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval, or otherwise compromise the potential development of the expanded access use. In this way, the proposed rule effectively balances the interests of those patient populations who would benefit from having greater access to investigational drugs, with the broader interests of society in having safe and effective new therapies approved for marketing and widely available.

The agency is also aware that allowing expanded access to investigational drugs before they are fully evaluated for safety may have adverse consequences for the seriously ill patients who receive them. The safeguards in the proposed rule are also designed with this concern in mind. Authorization of a particular expanded access use is generally contingent upon a number of factors, including some evidence of the drug's safety and effectiveness, obtaining the informed consent of the patient, approval of an IRB, and a careful assessment of the potential risks and benefits to the patient. In addition, the proposed rule would place limits on the scope and duration of certain types of expanded access use, require that sponsors of such INDs or protocols monitor the expanded access use and comply with safety and annual reporting requirements for INDs, and subject ongoing INDs or protocols to periodic reassessment. The agency believes these safeguards would adequately protect the safety and welfare of patients who would seek, and may benefit from, expanded access to investigational drugs.

*F. Costs of the Proposed Rule*

To the extent that the proposed rule results in an increase in the number of expanded access submissions, drug sponsors and physicians requesting investigational drugs on behalf of their patients will incur some additional costs. Because the proposed rule does not include any mandatory reporting requirements, the agency believes that the one-time costs associated with this rule will be negligible. Thus, the incremental burden imposed by this proposed rule will be in the form of additional annual or recurring costs associated with the increased number of expanded access submissions estimated previously in this document.

The agency estimates that preparation and submission of an individual patient expanded access submission would require a total of approximately 8 hours. This time burden would be divided among physicians (approximately 15 percent or 1.2 hours) and nurses, nurse practitioners, or medical administrators (approximately 85 percent or 6.8 hours). According to the U.S. Department of Labor, Bureau of Labor Statistics,[4] total employer costs per hour worked for employee compensation for registered nurses in the health care and social assistance sector was $36.21 as of June 24, 2004. Thus, the cost of the estimated 6.8 hours of nurse time required to prepare and submit an individual patient expanded access submission would be approximately $245 ($36.21 per hour x 6.8 hours).

Historically, most of the treatment use requests submitted to the agency have been prepared by physicians in the hematology/oncology specialty category. Data available on the Internet indicate that the median expected total compensation for a hematologist/oncologist in the United States was $287,016 as of October 2004.[5] This median total compensation figure corresponds to approximately $138 per hour ($137.99 = $287,016 / 2,080 hours). Thus the cost for the 1.2 hours of physician time required to prepare and submit an individual patient expanded access submission is about $165 ($138 per hour x 1.2 hours). Therefore, the agency estimates that the total cost to prepare and submit an individual patient expanded access submission would be about $410 ($410 = $245 + $165). Applying this cost figure to the number of additional individual patient expanded access submissions estimated previously in this document suggests the pattern of incremental annual costs summarized in table 4 of this document.

[4] See *http://www.bls.gov/news.release/ecec.toc.htm.* (FDA has verified the Web site address, but FDA is not responsible for any subsequent changes to the Web site after this document publishes in the **Federal Register**.)

[5] See *http://swz.salary.com/salarywizard/layouthtmls/swzl_compresult_national_HC07000054.html.* (FDA has verified the Web site address, but FDA is not responsible for any subsequent changes to the Web site after this document publishes in the **Federal Register**.)

TABLE 4.—NUMBER OF ADDITIONAL INDIVIDUAL PATIENT EXPANDED ACCESS SUBMISSIONS AND ESTIMATED ANNUAL COSTS

| Year After Implementation of Final Rule | Expected Increase in the Number of Individual Patient Submissions[1] | Expected Cost of Additional Individual Patient Submissions[2] |
|---|---|---|
| 1 | 132 to 264 | $54,120 to $108,240 |
| 2 | 198 to 329 | $81,180 to $134,890 |
| 3 | 264 to 395 | $108,240 to $161,950 |
| 4 | 264 to 395 | $108,240 to $161,950 |
| 5 | 264 to 395 | $108,240 to $161,950 |

[1]Based on increases in the number of individual patient expanded access submissions implied by the estimates presented in table 2 of this document.

[2]Based on an estimated cost of $410 per individual patient expanded access submission.

Preparation and submission of an intermediate size patient population expanded access IND or protocol is expected to require a total of about 120 hours of staff time. This time burden would be divided between a Director of Clinical Research, typically a medical doctor (approximately 50 percent or 60 hours), a Director of Regulatory Affairs (approximately 20 percent or 24 hours), and a Clinical Research Associate (approximately 30 percent or 36 hours).

Information available on the Internet and from industry sources suggests that the average salary for a Director of Clinical Research is about $200,000 per year.[6] Assuming that benefits represent approximately 30 percent of salary implies a total annual compensation estimate of $260,000. This translates into an estimated hourly total compensation figure of about $125 ($260,000 / 2,080 hours). Thus, the cost associated with the 60 hours of Clinical Research Director time required to prepare and submit an intermediate size patient population expanded access submission is approximately $7,500 (60 hours x $125).

Information available on the Internet and from industry sources also indicates that the average salary for a Director of Regulatory Affairs is approximately $160,000 per year.6 Assuming that benefits represent about 30 percent of this salary implies a total annual compensation estimate of $208,000. This translates into an estimated hourly total compensation figure of about $100 ($209,000 / 2,080 hours). Thus, the cost associated with the 24 hours of Director of Regulatory Affairs time required to prepare and submit an intermediate size patient population expanded access submission is approximately $2,400 (24 hours x $100).

Finally, information available on the Internet indicates that the median total compensation for a Clinical Research Associate is approximately $70,000 per year.[6] This translates into an estimated hourly total compensation figure of about $33.65 ($70,000 / 2,080 hours). Thus, the cost associated with the 36 hours of Clinical Research Associate time required to prepare and submit an intermediate size patient population expanded access submission is approximately $1,200 (36 hours x $33.65).

Based on the information presented, the agency estimates that the total cost to prepare and submit an intermediate size patient population expanded access submission would be approximately $11,100 ($11,100 = $7,500 + $2,400 + $1,200). Applying this figure to the increases in the number of intermediate size patient population expanded access submissions estimated previously in this document suggests the pattern of annual cost increases summarized in table 5 of this document.

TABLE 5.—NUMBER OF ADDITIONAL INTERMEDIATE SIZE PATIENT POPULATION EXPANDED ACCESS SUBMISSIONS AND ESTIMATED ANNUAL COSTS

| Year After Implementation of Final Rule | Expected Increase in the Number of Intermediate Size Patient Population Submissions[1] | Expected Cost of Additional Intermediate Size Patient Population Submissions[2] |
|---|---|---|
| 1 | 3 to 6 | $33,300 to $66,600 |
| 2 | 5 to 11 | $55,500 to $122,100 |
| 3 | 11 to 22 | $122,100 to $244,200 |
| 4 | 14 to 27 | $155,400 to $299,700 |

TABLE 5.—NUMBER OF ADDITIONAL INTERMEDIATE SIZE PATIENT POPULATION EXPANDED ACCESS SUBMISSIONS AND ESTIMATED ANNUAL COSTS—Continued

| Year After Implementation of Final Rule | Expected Increase in the Number of Intermediate Size Patient Population Submissions[1] | Expected Cost of Additional Intermediate Size Patient Population Submissions[2] |
|---|---|---|
| 5 | 14 to 27 | $155,400 to $299,700 |

[1]Based on increases in the number of intermediate size patient population expanded access submissions implied by the estimates presented in table 3 of this document.

[2]Based on an estimated cost of $11,000 per intermediate size patient population expanded access submission.

For reasons discussed previously in this document, the agency does not expect that the proposed rule will have an impact on the overall number of treatment INDs or treatment protocols. Therefore, FDA does not expect the provisions of this proposed rule regarding treatment INDs or treatment protocols to impose any incremental cost burden.

The total estimated annual and annualized cost burdens associated with this proposed rule are summarized in table 6 of this document.

TABLE 6.—COST SUMMARY

| Year After Implementation of Final Rule | One-Time Cost | Annual Cost | Annualized Cost[1] |
|---|---|---|---|
| 1 | $0 | $87,240 to $174,840 | $87,240 to $174,840 |
| 2 | $0 | $136,680 to $256,990 | $136,680 to $256,990 |
| 3 | $0 | $230,340 to $406,150 | $230,340 to $406,150 |
| 4 | $0 | $263,340 to $461,650 | $263,340 to $461,650 |
| 5 | $0 | $263,340 to $461,650 | $263,340 to $461,650 |

[1]Since estimated one-time costs are negligible, annual costs and annualized costs will be the same regardless of the interest rate.

For reasons discussed previously in this document, the agency expects that the total one-time costs of the proposed

[6]See *http://www.executivesonly.com/preview/exresults.cfm* under the Pharmaceutical specialty category. Viewed January 3, 2005. (FDA has verified the Web site address, but FDA is not responsible for any subsequent changes to the Web site after this document publishes in the Federal Register.)

rule will be negligible. FDA expects that the annual and annualized costs of this proposed rule will range from a low of about $87,000 to $175,000 in the first year following publication of any final rule based on this proposal, to a high of about $263,000 to $406,000 in the fourth and fifth years. These estimates suggest total annual and annualized costs for the proposed rule of between $1.0 and $1.8 million for the 5-year period following implementation of any final rule based on this proposal.

The agency expects that the estimated incremental cost burdens associated with this proposed rule are likely to be widely dispersed among affected entities for several reasons. First, given the historical volume of various types of treatment use submissions, the agency believes that a particular drug sponsor—or a physician acting on behalf of a patient—would submit a request for expanded access to investigational drugs fairly infrequently. Second, as noted previously, the proposed rule encourages the consolidation of multiple expanded access INDs or protocols for individual patients for a particular expanded access use under an intermediate size patient population expanded access IND or protocol. Such consolidation should, to some extent, offset incremental administrative burdens caused by increased patient access. Making the transition from multiple individual patient expanded access INDs or protocols to a single IND or protocol for an intermediate size patient population should reduce for sponsors the administrative burdens associated with making a drug available for expanded access use. In addition, provisions of the proposed rule are designed to minimize the amount of information and paperwork required to support a particular expanded access request. Physicians and drug sponsors would need to review the rule to become familiar with its provisions and to gather the evidence and information necessary to support an expanded access submission. However, in instances where a current IND already exists, a sponsor need only submit an amendment describing the information relevant to the expanded access protocol. Also, another sponsor or individual physician acting on behalf of a patient may, with the written permission of the original sponsor, reference information in the current IND already on file. The agency believes that a majority of expanded access submissions would have such a right of reference, either because the sponsor is also the drug developer or the developer would generally be willing to grant the request. To the extent that these provisions minimize the informational burden on potential sponsors or physicians, the proposed rule would enhance both efficiency and cost effectiveness.

### *G. Minimizing the Impact on Small Entities*

The agency does not believe the proposed rule will have a significant economic impact on a substantial number of small entities. Nevertheless, we recognize our uncertainty regarding the number and size distribution of affected entities, as well as the economic impact of the proposed rule on those entities. Therefore, the agency specifically requests detailed public comment on these issues.

Agency records indicate that the majority of submissions for treatment use of investigational drugs (about 78 percent) are submitted by commercial drug sponsors. Other entities making treatment use submissions include government agencies (approximately 14 percent), individual physicians (7 percent), and academic institutions (1 percent). Thus, the agency believes that the vast majority (92 percent) of sponsors of expanded access INDs or protocols (consisting of commercial drug sponsors or government agencies) would not be considered small entities. The remaining 8 percent of treatment use submissions are made by individual physicians and academic institutions that the agency believes would meet Small Business Administration small business criteria.

Of the average of 659 individual patient treatment use submissions submitted annually, very few are associated with commercial sponsors. The vast majority are submitted by individual physicians and various other unidentified sponsors for research purposes. Because nearly all individual patient treatment use submissions are made by various types of entities for research purposes, the agency believes that most of these entities would be classified as small entities.

Because there is currently no formal mechanism in place for tracking the other types of expanded access (e.g., intermediate size patient population submissions), no data exist that would allow the agency to identify the number of sponsors in this category that would qualify as small entities.

Thus, while highly uncertain, the agency believes that at least some of the entities submitting expanded access requests would qualify as small entities. Because of this uncertainty, the agency specifically requests detailed public comment regarding the number and size distribution of entities affected by the proposed rule. As discussed in section VII.E of this document, the agency expects that any incremental burden associated with the proposed rule will be small and widely dispersed among affected entities.

FDA considered several alternatives to the proposed rule. They are discussed in the following paragraphs.

#### 1. Do Not Propose Implementing Regulations for the Expanded Access Provisions of FDAMA

FDAMA revised the act to specifically authorize the use of investigational new drugs by licensed physicians to diagnose, monitor, or treat individual patients who have a serious disease or condition if, among other things, the physician determines that the person has no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition, and that the probable risk from the investigational drug is not greater than the probable risk from the disease or condition; and FDA determines that there is sufficient evidence of safety and effectiveness to support the use of the investigational drug. FDAMA also largely incorporated into the act FDA's current regulation concerning treatment INDs or treatment protocols under which large populations currently receive investigational drugs for treatment use. Because FDAMA did not require that FDA adopt implementing regulations, the agency could have chosen not to do so.

However, the agency believes that implementing regulations would further improve expanded access to investigational drugs for treatment use. One of the major criticisms about access to investigational drugs is that the criteria for authorizing access are unclear and that there is not broad knowledge among affected, or potentially affected, parties about the mechanisms or procedures to obtain access. FDA believes the proposed regulations are needed to address these concerns. The regulations provide to sponsors, patients, and licensed physicians who will be seeking investigational drugs for their patients clear direction about the criteria for authorizing expanded access and what information must be submitted to the agency to enable it to evaluate a proposed expanded access submission. Clearer direction and greater knowledge of the mechanisms and procedures for obtaining investigational drugs for expanded access use should reduce barriers to access.

2. Propose a Regulation Describing Only Individual Patient Expanded Access and the Treatment IND or Treatment Protocol

As discussed in the previous paragraphs, FDAMA specifically authorized the use of investigational new drugs by licensed physicians to diagnose, monitor, or treat individual patients in certain circumstances. FDAMA also essentially repeated FDA's current regulation concerning treatment INDs or treatment protocols under which large populations currently receive investigational drugs for treatment use.

FDA could have chosen to adopt regulations that described only these two categories of expanded access. However, FDA has had a long history of using an informal mechanism to make investigational drugs available to intermediate size patient populations. This mechanism would not be appropriate for either expanded access for individual patients or for treatment INDs or treatment protocols. The agency concluded that, consistent with the terminology of section 561(b)(4) of the act, it would be preferable to establish an intermediate category for expanded access, with additional criteria and monitoring requirements, that would be used for more than an individual patient, but fewer than the large numbers of patients in treatment INDs or treatment protocols.

In FDA's experience, there is often a need for a middle ground between an individual patient IND or protocol and a treatment IND or treatment protocol. For some drugs in development, there is considerable demand for expanded access before the use meets the criteria for a treatment IND or treatment protocol. There are also situations in which investigational drugs that are not being actively developed are the best available therapy for a significant number of patients and should be made available to patients under an expanded access process. In these situations, making the drug available under a series of individual patient expanded access INDs or protocols is burdensome on physicians, sponsors, and FDA, and makes it difficult to monitor the expanded access use to identify significant safety concerns such as serious adverse events.

Describing this intermediate category in regulation is also consistent with FDA's goal of maximizing awareness of expanded access programs by being more transparent about the processes for making drugs available for expanded access. As stated previously, FDA has used this intermediate category informally in the past and believes it will have reason to use this category in the future. Therefore, FDA believes it is appropriate to formalize and fully describe in regulation the intermediate expanded access category, as well as the two other categories of expanded access.

3. Propose a Regulation Describing More Than Three Expanded Access Categories

FDA also considered proposing a rule that would include more than three expanded access categories, but rejected this alternative. In internal discussions, FDA found that the distinctions between the proposed categories and the additional categories it considered were unclear. FDA was concerned that the additional categories would create confusion, rather than provide the clarity that is the goal of the proposed regulations. FDA concluded that the additional categories could be merged into the three proposed categories and that these categories will be able to provide access to investigational drugs in all situations FDA is likely to encounter.

## VIII. Paperwork Reduction Act of 1995

This proposed rule contains collections of information that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). "Collection of information" includes any request or requirement that persons obtain, maintain, retain, or report information to the agency, or disclose information to a third party or to the public (44 U.S.C. 3502(3) and 5 CFR 1320.3(c)). The title, description, and respondent description of the information collection are shown in the following paragraphs with an estimate of the annual reporting burden. Included in the estimate is the time for reviewing instructions, gathering and maintaining the data needed, and completing and reviewing the collection of information.

FDA invites comments on these topics: (1) Whether the proposed collection of information is necessary for proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques and other forms of information technology, when appropriate.

*Title*: Expanded Access to Investigational Drugs for Treatment Use

*Description*: The proposed rule would clarify existing regulations and expand on them by adding new types of expanded access for treatment use. Under the proposal, expanded access to investigational drugs would be available to individual patients, including in emergencies; to intermediate size patient populations; and to larger populations under a treatment protocol or IND. The proposed rule is intended to improve access to investigational drugs for patients with serious or immediately life-threatening diseases or conditions who lack other therapeutic options and may benefit from such therapies.

*A. The Proposed Rule*

1. Submission Requirements for All Expanded Access Uses

Proposed § 312.305(b) describes the submission requirements applicable to all types of expanded access. Proposed § 312.305(b)(1) states that an expanded access submission is required for each type of expanded access. The submission may be a new IND or a protocol amendment to an existing IND. Information required for a submission may be supplied by referring to pertinent information contained in an existing IND if the sponsor of the existing IND grants a right of reference to the IND.

Proposed § 312.305(b)(2) describes the expanded access submission requirements. The following items must be included:

- A cover sheet (Form FDA 1571) meeting the requirements of § 312.23(a);
- The rationale for the intended use of the drug, including a list of available therapeutic options that would ordinarily be tried before resorting to the investigational drug or an explanation of why the use of the investigational drug is preferable to the use of available therapeutic options;
- The criteria for patient selection; or, for an individual patient, a description of the patient's disease or condition, including recent medical history and previous treatments used for the disease or condition;
- The method of administration of the drug, dose, and duration of therapy;
- A description of the facility where the drug will be manufactured;
- Chemistry, manufacturing, and controls information adequate to ensure the proper identification, quality, purity, and strength of the investigational drug;
- Pharmacology and toxicology information adequate to conclude that

the drug is reasonably safe at the dose and duration proposed for expanded access use (ordinarily, information that would be adequate to permit clinical testing of the drug in a population of the size expected to be treated); and

- A description of clinical procedures, laboratory tests, or other monitoring necessary to evaluate the effects of the drug and minimize its risks.

2. Individual Patient Expanded Access

Proposed § 312.310(b) contains additional submission requirements that apply to use of an investigational drug for the treatment of an individual patient by a licensed physician. The expanded access submission must include information adequate to satisfy FDA that the criteria for all expanded access uses and those specific to individual patient expanded access have been met. The individual patient expanded access criteria are: (1) The physician must determine that the probable risk to the person from the investigational drug is not greater than the probable risk from the disease or condition and (2) FDA must determine that the patient cannot obtain the drug under another type of IND.

Proposed § 312.310(b)(1) states that if the drug is the subject of an existing IND, the expanded access submission may be made by a commercial sponsor or by a licensed physician. Proposed § 312.310(b)(2) states that a sponsor may satisfy the submission requirements by amending its existing IND to include an individual patient expanded access protocol. Proposed § 312.310(b)(3) states that a licensed physician may satisfy the submission requirements by obtaining a right of reference to pertinent information in the IND and providing any other required information not contained in the IND (usually only the information specific to the individual patient).

3. Intermediate Size Patient Populations

Proposed § 312.315(c) states that an expanded access submission for an intermediate size patient population must include information adequate to satisfy FDA that the criteria for all expanded access uses and those specific to intermediate size patient populations have been met. The intermediate size patient population criteria are: (1) There is enough evidence that the drug is safe at the dose and duration proposed for treatment use to justify a clinical trial of the drug in the approximate number of patients expected to receive the drug for treatment use and (2) there is at least preliminary clinical evidence of effectiveness of the drug or of a plausible pharmacologic effect of the drug to make expanded access use a reasonable therapeutic option in the anticipated patient population.

Proposed § 312.315(c) contains additional submission requirements that apply to use of an investigational drug for intermediate size patient populations. The expanded access submission must state whether the drug is being developed or is not being developed and describe the patient population to be treated. If the drug is not being actively developed, the sponsor must explain why the drug cannot currently be developed for the expanded access use and under what circumstances the drug could be developed. If the drug is being studied in a clinical trial, the sponsor must explain why the patients to be treated cannot be enrolled in the clinical trial and under what circumstances the sponsor would conduct a clinical trial in these patients.

4. Treatment IND or Protocol

Proposed § 312.320 describes the treatment IND or treatment protocol currently codified in §§ 312.34 and 312.35. Proposed § 312.320(b) states that the expanded access submission must include information adequate to satisfy FDA that the criteria for all expanded access uses and those specific to the treatment IND or protocol have been met. The criteria specific to a treatment IND or treatment protocol are: (1) The drug is being investigated in a controlled clinical trial designed to support a marketing application for the expanded access use or all clinical trials of the drug have been completed, (2) the sponsor is pursuing marketing approval of the drug for the expanded access use with due diligence, and (3) there is sufficient clinical evidence of safety and effectiveness to support the treatment use. Such evidence would ordinarily consist of data from phase 3 trials, but could consist of compelling data from completed phase 2 trials. When the expanded access use is for an immediately life-threatening disease or condition, the available scientific evidence, taken as a whole, could provide a reasonable basis to conclude that the investigational drug may be effective for the expanded access use and would not expose patients to an unreasonable and significant risk of illness or injury. This evidence would ordinarily consist of clinical data from phase 3 or phase 2 trials, but could be based on more preliminary clinical evidence.

*B. Estimates of Reporting Burden*

FDA's estimate of the amount of time required to complete an expanded access submission is based on the assumption that either the submission will be made by the drug developer or the submitter will have obtained a right of reference from the drug developer. FDA expects that, if finalized, the proposed rule would result in an increase in the number of submissions for expanded access for individual patients and for intermediate size patient populations.

1. Individual Patient Expanded Access

From 1997 to 2005, FDA received on average approximately 659 submissions for the treatment use of investigational drugs by individual patients per year. This estimate is based on FDA records on the number of individual patient IND submissions (primarily from physicians) and a survey of review divisions on the prevalence of individual patient protocol exception submissions received from commercial drug sponsors. The agency expects an increase in the number of individual patient expanded access submissions as a result of the proposed rule because the proposed rule would increase awareness of the option for individual patients to gain access to investigational drugs and decrease the perceived difficulty of obtaining such access. FDA anticipates that the increase in individual patient expanded access INDs or protocols would be greatest in the years immediately following implementation of a final rule and would at some point level off, or possibly even decline. This leveling off or decline would occur when a significant volume of individual patient expanded access INDs or protocols have accumulated for a variety of drugs, and the individual patient expanded access INDs or protocols for those drugs are then replaced with intermediate size patient population expanded access INDs or protocols that enroll multiple subjects.

The agency estimates that preparation and submission of an individual patient expanded access IND or protocol submission would require a total of approximately 8 hours.

2. Intermediate Size Patient Population Expanded Access

Although intermediate size patient population expanded access INDs or protocols have not previously been described in regulation, investigational drugs have been made available informally for treatment use to such populations. Based on an internal survey of review divisions, FDA

estimates that, for the period 2000 through 2002, it received approximately 55 submissions per year that would be considered expanded access for an intermediate size patient population under the proposed criteria. The agency anticipates that this proposed rule would increase the number of such submissions because there will be greater awareness of this option. In addition, the anticipated increase in volume of submissions for expanded access for individual patients discussed previously is expected to increase the number of submissions for expanded access for intermediate size patient populations because the proposed rule encourages the consolidation of multiple individual patient INDs or protocols for a given expanded access use.

Information provided by FDA review division staff indicates that preparation and submission of an intermediate size patient population IND would require a total of about 120 hours of staff time.

3. Treatment IND or Treatment Protocol

The agency does not expect that the proposed rule will have an impact on the overall number of treatment INDs or treatment protocols because this type of expanded access is already established in FDA's regulations. Therefore, FDA does not expect the provisions of this proposed rule regarding treatment INDs or treatment protocols to impose any increased paperwork burden.

4. Capital Costs

There are capital costs associated with this proposed rulemaking. These costs are discussed in section VII of this document, "Analysis of Economic Impacts."

*Description of Respondents*: Licensed physicians and manufacturers, including small business manufacturers. Table 7 of this document presents the annualized reporting burden for the total number of expanded access submissions, broken down by type of expanded access use. The figures in the table are based on the analysis of economic impacts (section VII of this document) and are derived by averaging the projected number of submissions for the first 3 years after implementation of a final rule based on this proposed rule.

TABLE 7.—ESTIMATED REPORTING BURDEN

| 21 CFR section | No. of Respondents | No. of Responses per Respondent | Total Responses | Hours per Response | Total Hours |
|---|---|---|---|---|---|
| 312.310(b) Individual patient expanded access and 310.305(b) submission requirements generally | 1,054 | 1 | 1,054 | 8 | 8,432 |
| 312.315(c) Intermediate size patient population expanded access and 310.305(b) submission requirements generally | 77 | 1 | 77 | 120 | 9,240 |
| 312.320 Treatment IND or protocol and 310.305(b) submission requirements generally | 5 | 1 | 5 | 300 | 1,500 |
| Total | | | | | 19,172 |

In compliance with section 3507(d) of the Paperwork Reduction Act of 1995 (44 U.S.C. 3507(d)), the agency has submitted the information collection provisions of this proposed rule to OMB for review. Interested persons are requested to send comments regarding information collection (see **ADDRESSES**).

## IX. Request for Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this document. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

## X. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. FDA has tentatively determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency has tentatively concluded that the rule does not contain policies that have federalism implications as defined in the order and, consequently, a federalism summary impact statement is not required.

## List of Subjects in 21 CFR Part 312

Drugs, Exports, Imports, Investigations, Labeling, Medical research, Reporting and recordkeeping requirements, and Safety.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 312 be amended as follows:

## PART 312—INVESTIGATIONAL NEW DRUG APPLICATION

1. The authority citation for 21 CFR part 312 is revised to read as follows:

**Authority:** 21 U.S.C. 321, 331, 351, 352, 353, 355, 360bbb, 371; 42 U.S.C. 262.

**§ 312.34 [Removed]**

2. Section 312.34 *Treatment use of an investigational new drug* is removed.

**§ 312.35 [Removed]**

3. Section 312.35 *Submissions for treatment use* is removed.

**§ 312.36 [Removed]**

4. Section 312.36 *Emergency use of an investigational new drug (IND)* is removed.

5. Section 312.42 is amended by revising paragraph (b)(3) to read as follows:

**§ 312.42 Clinical holds and requests for modification.**

* * * * *

(b) * * *

(3) *Clinical hold of an expanded access IND or expanded access protocol.* FDA may place an expanded access IND or expanded access protocol on clinical hold under the following conditions:

(i) *Proposed use.* FDA may place a proposed expanded access IND or treatment use protocol on clinical hold if it is determined that:

(A) The pertinent criteria in subpart I of this part for permitting the expanded access use to begin are not satisfied; or

(B) The expanded access IND or expanded access protocol does not comply with the requirements for expanded access submissions in subpart I of this part.

(ii) *Ongoing use.* FDA may place an ongoing expanded access IND or expanded access protocol on clinical hold if it is determined that the pertinent criteria in subpart I of this part for permitting the expanded access are no longer satisfied.

* * * * *

6. Part 312 is amended by adding and reserving subpart H, and by adding subpart I, consisting of §§ 312.300 through 312.320, to read as follows:

**Subpart H—[Reserved]**

**Subpart I—Expanded Access to Investigational Drugs for Treatment Use**

Sec.



**§ 312.300 General.**

(a) *Scope.* This subpart contains the requirements for the use of investigational new drugs when the primary purpose is to diagnose, monitor, or treat a patient's disease or condition. The aim of this subpart is to facilitate the availability of investigational new drugs to seriously ill patients when there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the patient's disease or condition.

(b) *Definition.* In this subpart, the term immediately life-threatening disease means a stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.

**§ 312.305 Requirements for all expanded access uses.**

The criteria, submission requirements, safeguards, and beginning treatment information set out in this section apply to all expanded access uses described in this subpart. Additional criteria, submission requirements, and safeguards that apply to specific types of expanded access are described in §§ 312.310 through 312.320.

(a) *Criteria.* FDA must determine that:

(1) The patient or patients to be treated have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;

(2) The potential patient benefit justifies the potential risks of the treatment use and those potential risks are not unreasonable in the context of the disease or condition to be treated; and

(3) Providing the investigational drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use.

(b) *Submission.* (1) An expanded access submission is required for each type of expanded access described in this subpart. The submission may be a new IND or a protocol amendment to an existing IND. Information required for a submission may be supplied by referring to pertinent information contained in an existing IND if the sponsor of the existing IND grants a right of reference to the IND.

(2) The expanded access submission must include:

(i) A cover sheet (Form FDA 1571) meeting the requirements of § 312.23(a);

(ii) The rationale for the intended use of the drug, including a list of available therapeutic options that would ordinarily be tried before resorting to the investigational drug or an explanation of why the use of the investigational drug is preferable to the use of available therapeutic options;

(iii) The criteria for patient selection; or, for an individual patient, a description of the patient's disease or condition, including recent medical history and previous treatments of the disease or condition;

(iv) The method of administration of the drug, dose, and duration of therapy;

(v) A description of the facility where the drug will be manufactured;

(vi) Chemistry, manufacturing, and controls information adequate to ensure the proper identification, quality, purity, and strength of the investigational drug;

(vii) Pharmacology and toxicology information adequate to conclude that the drug is reasonably safe at the dose and duration proposed for expanded access use (ordinarily, information that would be adequate to permit clinical testing of the drug in a population of the size expected to be treated); and

(viii) A description of clinical procedures, laboratory tests, or other monitoring necessary to evaluate the effects of the drug and minimize its risks.

(3) The expanded access submission and its mailing cover must be plainly marked "EXPANDED ACCESS SUBMISSION." If the expanded access submission is for a treatment IND or treatment protocol, the applicable box on Form FDA 1571 must be checked.

(c) *Safeguards.* The responsibilities of sponsors and investigators set forth in subpart D of this part are applicable to expanded access use under this subpart as described in this paragraph.

(1) A licensed physician under whose immediate direction an investigational drug is administered or dispensed for an expanded access use under this subpart is considered an *investigator*, for purposes of this part, and must comply with the responsibilities for investigators set forth in subpart D of this part to the extent they are applicable to the expanded access use.

(2) An individual or entity that submits an expanded access IND or protocol under this subpart is considered a *sponsor*, for purposes of this part, and must comply with the responsibilities for sponsors set forth in subpart D of this part to the extent they are applicable to the expanded access use.

(3) A licensed physician under whose immediate direction an investigational drug is administered or dispensed, and who submits an IND for expanded access use under this subpart is considered a *sponsor-investigator*, for purposes of this part, and must comply with the responsibilities for sponsors and investigators set forth in subpart D of this part to the extent they are applicable to the expanded access use.

(4) *Investigators.* In all cases of expanded access, investigators are responsible for reporting adverse drug experiences to the sponsor, ensuring that the informed consent requirements of part 50 of this chapter are met, ensuring that IRB review of the expanded access use is obtained in a manner consistent with the requirements of part 56 of this chapter, and maintaining accurate case histories and drug disposition records and retaining records in a manner consistent with the requirements of § 312.62. Depending on the type of expanded access, other investigator's responsibilities under subpart D may also apply.

(5) *Sponsors.* In all cases of expanded access, sponsors are responsible for submitting IND safety reports and annual reports (when the IND or protocol continues for 1 year or longer) to FDA as required by §§ 312.32 and

312.33, ensuring that licensed physicians are qualified to administer the investigational drug for the expanded access use, providing licensed physicians with the information needed to minimize the risk and maximize the potential benefits of the investigational drug (e.g., providing the investigator's brochure, if there is one), maintaining an effective IND for the expanded access use, and maintaining adequate drug disposition records and retaining records in a manner consistent with the requirements of § 312.57. Depending on the type of expanded access, other sponsor's responsibilities under subpart D may also apply.

(d) *Beginning treatment.* (1) *INDs.* An expanded access IND goes into effect 30 days after FDA receives the IND or on earlier notification by FDA that the expanded access use may begin.

(2) *Protocols.* With the following exceptions, expanded access use under a protocol submitted under an existing IND may begin as described in § 312.30(a).

(i) Expanded access use under the emergency procedures described in § 312.310(d) may begin when the use is authorized by the FDA reviewing official.

(ii) Expanded access use under § 312.320 may begin 30 days after FDA receives the protocol or upon earlier notification by FDA that use may begin.

(3) *Clinical holds.* FDA may place any expanded access IND or protocol on clinical hold as described in § 312.42.

**§ 312.310 Individual patients, including for emergency use.**

Under this section, FDA may permit an investigational drug to be used for the treatment of an individual patient by a licensed physician.

(a) *Criteria.* The criteria in § 312.305(a) must be met; and the following determinations must be made:

(1) The physician must determine that the probable risk to the person from the investigational drug is not greater than the probable risk from the disease or condition; and

(2) FDA must determine that the patient cannot obtain the drug under another type of IND or protocol.

(b) *Submission.* The expanded access submission must include information adequate to demonstrate that the criteria in § 312.305(a) and paragraph (a) of this section have been met. The expanded access submission must meet the requirements of § 312.305(b).

(1) If the drug is the subject of an existing IND, the expanded access submission may be made by the sponsor or by a licensed physician.

(2) A sponsor may satisfy the submission requirements by amending its existing IND to include a protocol for individual patient expanded access.

(3) A licensed physician may satisfy the submission requirements by obtaining from the sponsor permission for FDA to refer to any information in the IND that would be needed to support the expanded access request (right of reference) and by providing any other required information not contained in the IND (usually only the information specific to the individual patient).

(c) *Safeguards.* (1) Treatment is generally limited to a single course of therapy for a specified duration unless FDA expressly authorizes multiple courses or chronic therapy.

(2) At the conclusion of treatment, the licensed physician or sponsor must provide a written summary of the results of the expanded access use, including unexpected adverse effects.

(3) FDA may require sponsors to monitor an individual patient expanded access use if the use is for an extended duration.

(4) When a significant number of similar individual patient expanded access requests have been submitted, FDA may ask the sponsor to submit an IND or protocol for the use under § 312.315 or § 312.320.

(d) *Emergency procedures.* If there is an emergency that requires the patient to be treated before a written submission can be made, FDA may authorize the expanded access use to begin without a written submission. The FDA reviewing official may authorize the emergency use by telephone.

(1) Emergency expanded access use may be requested by telephone, facsimile, or other means of electronic communications. For investigational biological drug products regulated by the Center for Biologics Evaluation and Research, the request should be directed to the Office of Communication, Training, and Manufacturers Assistance, Center for Biologics Evaluation and Research, 301–827–2000, e-mail: *octma@cber.fda.gov.* For all other investigational drugs, the request for authorization should be directed to the Division of Drug Information, Center for Drug Evaluation and Research, 301–827–4570, e-mail: *druginfo@cder.fda.gov.* After normal working hours, the request should be directed to the FDA Office of Emergency Operations, 301–443–1240, e-mail: *emergency.operations@fda.hhs.gov.*

(2) The licensed physician or sponsor must explain how the expanded access use will meet the requirements of §§ 312.305 and 312.310 and must agree to submit an expanded access submission within 5 working days of FDA's authorization of the use.

**§ 312.315 Intermediate-size patient populations.**

Under this section, FDA may permit an investigational drug to be used for the treatment of a patient population smaller than that typical of a treatment IND or treatment protocol. FDA may ask a sponsor to consolidate expanded access under this section when the agency has received a significant number of requests for individual patient expanded access to an investigational drug for the same use.

(a) *Need for expanded access.* Expanded access under this section may be needed in the following situations:

(1) *Drug not being developed.* The drug is not being developed, for example, because the disease or condition is so rare that the sponsor is unable to recruit patients for a clinical trial.

(2) *Drug being developed.* The drug is being studied in a clinical trial, but patients requesting the drug for expanded access use are unable to participate in the trial. For example, patients may not be able to participate in the trial because they have a different disease or stage of disease than the one being studied or otherwise do not meet the enrollment criteria, because enrollment in the trial is closed, or because the trial site is not geographically accessible.

(3) *Approved or related drug.* (i) The drug is an approved drug product that is no longer marketed for safety reasons or is unavailable through marketing due to failure to meet the conditions of the approved application, or

(ii) The drug contains the same active moiety as an approved drug product that is unavailable through marketing due to failure to meet the conditions of the approved application or a drug shortage.

(b) *Criteria.* The criteria in § 312.305(a) must be met; and FDA must determine that:

(1) There is enough evidence that the drug is safe at the dose and duration proposed for expanded access use to justify a clinical trial of the drug in the approximate number of patients expected to receive the drug under expanded access; and

(2) There is at least preliminary clinical evidence of effectiveness of the drug, or of a plausible pharmacologic effect of the drug to make expanded access use a reasonable therapeutic option in the anticipated patient population.

(c) *Submission.* The expanded access submission must include information

adequate to satisfy FDA that the criteria in § 312.305(a) and paragraph (b) of this section have been met. The expanded access submission must meet the requirements of § 312.305(b). In addition:

(1) The expanded access submission must state whether the drug is being developed or is not being developed and describe the patient population to be treated.

(2) If the drug is not being actively developed, the sponsor must explain why the drug cannot currently be developed for the expanded access use and under what circumstances the drug could be developed.

(3) If the drug is being studied in a clinical trial, the sponsor must explain why the patients to be treated cannot be enrolled in the clinical trial and under what circumstances the sponsor would conduct a clinical trial in these patients.

(d) *Safeguards.* (1) Upon review of the IND annual report, FDA will determine whether it is appropriate for the expanded access to continue under this section.

(i) If the drug is not being actively developed or if the expanded access use is not being developed (but another use is being developed), FDA will consider whether it is possible to conduct a clinical study of the expanded access use.

(ii) If the drug is being actively developed, FDA will consider whether providing the investigational drug for expanded access use is interfering with the clinical development of the drug.

(iii) As the number of patients enrolled increases, FDA may ask the sponsor to submit an IND or protocol for the use under § 312.320.

(2) The sponsor is responsible for monitoring the expanded access protocol to ensure that licensed physicians comply with the protocol and the regulations applicable to investigators.

**§ 312.320 Treatment IND or treatment protocol.**

Under this section, FDA may permit an investigational drug to be used for widespread treatment use.

(a) *Criteria.* The criteria in § 312.305(a) must be met, and FDA must determine that:

(1) *Trial status.* (i) The drug is being investigated in a controlled clinical trial under an IND designed to support a marketing application for the expanded access use, or

(ii) All clinical trials of the drug have been completed; and

(2) *Marketing status.* The sponsor is actively pursuing marketing approval of the drug for the expanded access use with due diligence; and

(3) *Evidence.* (i) When the expanded access use is for a serious disease or condition, there is sufficient clinical evidence of safety and effectiveness to support the expanded access use. Such evidence would ordinarily consist of data from phase 3 trials, but could consist of compelling data from completed phase 2 trials; or

(ii) When the expanded access use is for an immediately life-threatening disease or condition, the available scientific evidence, taken as a whole, provides a reasonable basis to conclude that the investigational drug may be effective for the expanded access use and would not expose patients to an unreasonable and significant risk of illness or injury. This evidence would ordinarily consist of clinical data from phase 3 or phase 2 trials, but could be based on more preliminary clinical evidence.

(b) *Submission.* The expanded access submission must include information adequate to satisfy FDA that the criteria in § 312.305(a) and paragraph (a) of this section have been met. The expanded access submission must meet the requirements of § 312.305(b).

(c) *Safeguard.* The sponsor is responsible for monitoring the treatment protocol to ensure that licensed physicians comply with the protocol and the regulations applicable to investigators.

Dated: December 6, 2006.

**Jeffrey Shuren,**

*Assistant Commissioner for Policy.*

[FR Doc. 06–9684 Filed 12–11–06; 10:01 am]

BILLING CODE 4160–01–S

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## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

### 21 CFR Part 312

**[Docket No. 2006N–0061]**

**RIN 0910–AF13**

## Charging for Investigational Drugs

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Proposed rule.

**SUMMARY:** The Food and Drug Administration (FDA) is proposing to amend its investigational new drug application (IND) regulation concerning charging patients for investigational new drugs. FDA is proposing to revise the current charging regulation to clarify the circumstances in which charging for an investigational drug in a clinical trial is appropriate, to set forth criteria for charging for an investigational drug for the different types of expanded access for treatment use described in the agency's proposed rule on expanded access for treatment use of investigational drugs published elsewhere in this issue of the **Federal Register**, and to clarify what costs can be recovered for an investigational drug. The proposed rule is intended to permit charging for a broader range of investigational and expanded access uses than is explicitly permitted in current regulations.

**DATES:** Submit written or electronic comments by March 14, 2007. Submit written comments on the information collection requirements by January 16, 2007.

**ADDRESSES:** You may submit comments, identified by Docket No. 2006N–0061 and/or RIN number 0910–AF13, by any of the following methods:

*Electronic Submissions*

Submit electronic comments in the following ways:

- Federal eRulemaking Portal: *http://www.regulations.gov*. Follow the instructions for submitting comments.
- Agency Web site: *http://www.fda.gov/dockets/ecomments*. Follow the instructions for submitting comments on the agency Web site.

*Written Submissions*

Submit written submissions in the following ways:

- FAX: 301–827–6870.
- Mail/Hand delivery/Courier [For paper, disk, or CD–ROM submissions]: Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

To ensure more timely processing of comments, FDA is no longer accepting comments submitted to the agency by e-mail. FDA encourages you to continue to submit electronic comments by using the Federal eRulemaking Portal or the agency Web site, as described in the *Electronic Submissions* portion of this paragraph.

*Instructions*: All submissions received must include the agency name and Docket No(s). and Regulatory Information Number (RIN) (if a RIN number has been assigned) for this rulemaking. All comments received may be posted without change to *http://www.fda.gov/ohrms/dockets/default.htm*, including any personal information provided. For additional information on submitting comments, see the "Comments" heading of the **SUPPLEMENTARY INFORMATION** section of this document.

*Docket*: For access to the docket to read background documents or

# EXHIBIT 4

PHARMACEUTICALS AND BIOTECHNOLOGY May 04, 2008 7:41 PM ET

# PTC Therapeutics, Inc.

Snapshot People

## COMPANY OVERVIEW

PTC Therapeutics, Inc., a biopharmaceutical company, focuses on the discovery, development, and commercialization of orally administered, proprietary small-molecule drugs that target post-transcriptional control processes. Its pipeline of clinical and preclinical product candidates addresses multiple indications, including genetic disorders, oncology, and infectious diseases. The company's lead product candidates include PTC124, a Phase II clinical trial product for the treatment of cystic fibrosis and Duchenne muscular dystrophy patients with a specific type of genetic mutation; PTC299, a preclinical stage product for the treatment of cancer; and Hepatitis C development program. PTC Therape...

Detailed Description

100 Corporate Court
South Plainfield, NJ 07080-2449
United States

Phone: 908-222-7000
Fax: 908-222-7231
www.ptcbio.com

Founded in 1998
91 Employees

## KEY EXECUTIVES

**Dr. Stuart W. Peltz**
Co-Founder
Age: 47

**Dr. William D. Ju**
Chief Operating Officer
Age: 50

**Dr. Langdon Miller**
Chief Medical Officer

**Dr. John Babiak**
Senior Vice President of Drug Discovery Technologies
Age: 50

**Mr. Mark E. Boulding**
Senior Vice President
Age: 46

Compensation as of Fiscal Year 2007.

## KEY DEVELOPMENTS

### PTC Therapeutics Announces Initiation of Phase 2b Registration-directed Clinical Trial of Ptc124 in Duchenne/Becker Muscular Dystrophy
04/23/2008

PTC Therapeutics Inc. announced the initiation of an international pivotal trial of PTC124 in patients with Duchenne/Becker muscular dystrophy (DMD/BMD) due to a nonsense mutation. The primary objective of this registration-directed Phase 2b trial is to demonstrate the efficacy of PTC124 as measured by improvements in the walking ability of patients with this progressive genetic disease. Patients with DMD and BMD are boys and young men who lack dystrophin, a protein that is critical to the structural stability of muscle fibers. Patients develop progressive muscle weakness that leads to loss of ambulation, wheelchair dependency, and eventual decline in respiratory and cardiac function. It is estimated that one in 10 DMD patients are likely to have a Becker presentation, a milder form of the disease that is associated with later manifestation of symptoms. In essence, DMD and BMD represent a continuum of the same disease.

### PTC Therapeutics Announces Publication of Preclinical Data in PNAS
02/4/2008

PTC Therapeutics Inc. announced the publication of new preclinical data in the February 12, 2008 edition of the Proceedings of the National Academy of Sciences (PNAS) which show that PTC124, a novel drug designed to bypass nonsense mutations, was active in a preclinical model of cystic fibrosis (CF). These results support and add to research published last year in the journal Nature, which demonstrated the activity of PTC124 in a preclinical model of Duchenne muscular dystrophy (DMD). PTC124 has demonstrated pharmacodynamic proof of concept in Phase 2a clinical trials in nonsense-mutation-mediated CF and DMD.

### PTC Therapeutics Presents Encouraging Phase 1 Results of its Novel VEGF Inhibitor, PTC299, at 30th Annual San Antonio Breast Cancer Symposium
12/17/2007

PTC Therapeutics Inc. announced the presentation of preclinical and Phase 1 data regarding PTC299, its novel, internally discovered, vascular endothelial growth factor (VEGF) inhibitor. PTC299 is an orally bioavailable

investigational drug which is designed to inhibit the production of VEGF in tumors, acting upstream of current anti-angiogenic agents that function at the site of the VEGF receptor. The preclinical and clinical data presented formed the basis for the recent initiation of a Phase 1b/2 clinical trial of PTC299 in patients with advanced breast cancer.



RECENT PRIVATE COMPANIES TRANSACTIONS

| Type / Date | Target |
|---|---|
| Private Placement September 13, 2007 | – |



MOST SEARCHED PRIVATE COMPANIES

| | |
|---|---|
| Beiersdorf AG | Europe |
| NYC2012, Inc. | United States |
| [illegible] | United States |
| I & H Brown Limited | Europe |

# EXHIBIT 5

▼ **Leadership**

▼ Senior Management

Stuart W. Peltz, Ph.D.

William D. Ju, M.D.

Langdon L. Miller, M.D.

William Baird, III

Neil Almstead, Ph.D.

John Babiak, Ph.D.

Mark E. Boulding

Joseph M. Colacino, Ph.D.

Cláudia Hirawat

Manal Morsy, M.D., Ph.D.

Theresa Natalicchio

▶ Board of Directors

▶ Scientific Advisory Board

▶ **Collaborations**

▶ **Working at PTC**

# Cláudia Hirawat

**Sr. Vice President, Corporate Development**
Cláudia Hirawat is responsible for Business and Corporate Development spearheading PTC's collaborations. Ms. Hirawat joined PTC in 2000 as the company's seventh employee. Partnering with the CEO and the senior management team, Ms. Hirawat played a key role in building PTC and was directly involved in fundraising, operational directives, public and investor relations, patient and professional advocacy and commercial development. Prior to PTC, Ms. Hirawat was a Vice President at LedbetterStevens, a management consulting and senior-level retained search firm in New York focused exclusively in the biopharmaceutical area. Ms. Hirawat was at LedbetterStevens for five years and had responsibilities for projects for a variety of clients including: Pfizer, Pharmacia, Bristol Myers Squibb Co., Celera Genomics, Coelacanth Corp., SpotFire, IBM Consulting/The Wilkerson Group and The Boston Consulting Group.

# EXHIBIT 6

**MANAGEMENT'S DISCUSSION AND ANALYSIS OF**

**FINANCIAL CONDITION AND RESULTS OF OPERATIONS**

You should read the following discussion and analysis of our financial condition and results of operations together with our financial statements and the related notes appearing at the end of this prospectus. Some of the information contained in this discussion and analysis or set forth elsewhere in this prospectus, including information with respect to our plans and strategy for our business and related financing, includes forward-looking statements that involve risks and uncertainties. You should read the "Risk Factors" section of this prospectus for a discussion of important factors that could cause actual results to differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

Overview

We are a biopharmaceutical company focused on the discovery, development and commercialization of orally administered, proprietary small-molecule drugs that target post-transcriptional control processes. Our current pipeline of clinical and preclinical product candidates addresses multiple indications, including genetic disorders, oncology and infectious diseases. Our three most advanced product development programs are:

- PTC124 for genetic disorders. We are currently conducting two Phase 2 clinical trials of PTC124 in patients with cystic fibrosis and one Phase 2 clinical trial of PTC124 in patients with Duchenne muscular dystrophy in cases in which a nonsense mutation is the cause of the disease. We have conducted an interim analysis of data from 15 patients who have completed their participation in our cystic fibrosis trials.

- PTC299 for oncology. In April 2006, we expect to commence a Phase 1a clinical trial of PTC299 in healthy volunteers in Belgium. If this Phase 1a trial is successful, we plan to initiate a Phase 1b clinical trial of PTC299 in late 2006 in patients with advanced solid tumors whose disease has progressed during therapy or for whom there is no effective therapy available.

- Hepatitis C development program. In March 2006, we entered into a collaboration with Schering-Plough Corporation for the commercialization of our compounds for the potential treatment of hepatitis C.

We are also conducting discovery programs focused on identifying new treatments for multiple therapeutic areas, including bacterial infections, anemia and musculoskeletal conditions.

We have generated significant losses as we have progressed our lead product candidates into clinical development and expect to continue to generate losses

as we continue the clinical development of PTC124 and PTC299. Our net loss for 2005 was $22.9 million. As of December 31, 2005, we had a deficit accumulated during the development stage of $92.1 million.

Financial Operations Overview

Revenues

To date, we have not generated any product sale revenues. We have funded our operations primarily through the sale of equity securities, capital lease and equipment financings, foundation and government grants and collaboration revenues. Our revenues for 2005 were approximately $5.0 million, consisting primarily of grant revenues.

We have received grant funding from a variety of foundations and government agencies, including Cystic Fibrosis Foundation Therapeutics, Inc., the Muscular Dystrophy Association, Parent Project Muscular Dystrophy and the National Institutes of Health. Grants are awarded on a project basis. We recognize grant revenues as we receive funding or when preclinical, clinical or regulatory milestones are met.

In March 2006, we entered into a collaboration and license agreement with a subsidiary of Schering-Plough Corporation under which we and Schering-Plough are collaborating in the discovery, development and





commercialization of compounds for the treatment of HCV and other viral diseases. Pursuant to the collaboration agreement, Schering-Plough paid us an upfront non-refundable payment of $12.0 million. Our agreement with Schering-Plough provides for a research collaboration, in connection with which Schering-Plough has agreed to provide us with funding, based on a full-time equivalent rate, for an agreed upon number of full-time equivalent scientific or research and development personnel that we dedicate to the research program. The initial research term is three years. Schering-Plough has two options to extend the research term for an additional term of one year per option. Schering-Plough can terminate the research term in specified circumstances. Schering-Plough is responsible for worldwide clinical development and commercialization of any compounds that it elects to advance from our research collaboration. We are eligible to receive more than $200 million in payments if we achieve specified development, regulatory and sales milestones. We are also entitled to royalties on sales of products developed pursuant to the collaboration, with the royalty percentage based on specified thresholds of worldwide net product sales.

In December 2005, we entered into a research collaboration and exclusive option agreement with Bausch & Lomb under which Bausch & Lomb is evaluating compounds in our anti-angiogenesis program for the purpose of identifying potential candidates for development by Bausch & Lomb for the treatment of ophthalmic diseases associated with angiogenesis, including macular degeneration. Under the terms of the agreement, we granted Bausch & Lomb exclusive options to license selected compounds. Bausch & Lomb has one year from the date of the agreement to exercise any such option. In exchange for the one-year options, Bausch & Lomb paid us an upfront non-refundable option grant fee of $300,000 and agreed to provide us with research funding during the option term to compensate us for completing agreed research. Bausch & Lomb has the right to extend the option term with respect to certain specified compounds for an additional six months in exchange for an extension fee. As of December 31, 2005, we had recognized $50,000 of revenue pursuant to the agreement.

Research and Development Expense

Research and development expenses consist of the costs associated with our research activities, as well as the costs associated with our drug discovery efforts, conducting preclinical studies and clinical trials, manufacturing development efforts and activities related to regulatory filings. Our research and development expenses consist of:

- external research and development expenses incurred under agreements with third-party contract research organizations and investigative sites, third-party manufacturing organizations and consultants;

- employee-related expenses, which include salaries and benefits for the personnel involved in our drug discovery and development activities; and

- facilities, depreciation and other allocated expenses, which include direct and allocated expenses for rent and maintenance of facilities, depreciation of leasehold improvements and equipment, and laboratory and

other supplies.

We use our employee and infrastructure resources across multiple research projects, including our drug development programs. We track expenses related to our clinical programs on a per project basis. Accordingly, we allocate internal employee-related and infrastructure costs, as well as third-party costs, to each clinical program. We do not allocate expenses related to preclinical programs.



**Table of Contents**

The following table summarizes our principal product development programs, including the related stages of development for each product candidate in development and the research and development expenses allocated to each clinical product candidate. The information in the column labeled "Estimated Completion of Current Trial" is our estimate of the timing of completion of the current clinical trial or trials for the particular product candidate. The actual timing of completion could differ materially from the estimates provided in the table.

| Product Candidate | Indication | Phase of Development | Estimated Completion of Current Trial | Year Ended December 31, 2003 | 2004 | 2005 |
|---|---|---|---|---|---|---|
| | | | | (in thousands) | | |
| Clinical development: | | | | | | |
| PTC124 | Cystic Fibrosis; Duchenne Muscular Dystrophy | Phase 2 | 2006 | $ 2,642 | $ 6,018 | $ 5,132 |
| PTC299 | Cancer | Phase 1a | 2006 | - | 83 | 2,021 |
| Total clinical development | | | | 2,642 | 6,101 | 7,153 |
| Research and preclinical | | | | 15,053 | 13,969 | 13,970 |
| Total research and development | | | | $ 17,695 | $ 20,070 | $ 21,123 |

The successful development of our product candidates is highly uncertain. At this time, we cannot reasonably estimate or know the nature, timing and estimated costs of the efforts that will be necessary to complete the remainder of the development of, or the period, if any, in which material net cash inflows may commence from, PTC124, PTC299 or any of our preclinical product candidates. This is due to the numerous risks and uncertainties associated with developing drugs, including the uncertainty of:

- the scope, rate of progress and expense of our clinical trials and other research and development activities;
- the potential benefits of our product candidates over other therapies;
- our ability to market, commercialize and achieve market acceptance for any of our product candidates that we are developing or may develop in the future;
- future clinical trial results;
- the terms and timing of regulatory approvals; and
- the expense of filing, prosecuting, defending and enforcing any patent claims and other intellectual property rights.

A change in the outcome of any of these variables with respect to the

development of a product candidate could mean a significant change in the costs and timing associated with the development of that product candidate. For example, if the FDA or other regulatory authority were to require us to conduct clinical trials beyond those which we currently anticipate will be required for the completion of clinical development of a product candidate or if we experience significant delays in enrollment in any our clinical trials, we could be required to expend significant additional financial resources and time on the completion of clinical development.

General and Administrative Expense

General and administrative expense consists primarily of salaries and other related costs for personnel, including stock-based compensation expenses, in our executive, legal, business development, finance, accounting information technology and human resource functions. Other general and administrative expenses include facility-related costs not otherwise included in research and development expense; advertising and





promotional expenses; costs associated with industry and trade shows; and professional fees for legal services, including patent-related expenses, and accounting services.

We expect that general and administrative expense will increase in 2006 and in future periods as a result of increased payroll, expanded infrastructure, increased consulting, legal, accounting and investor relations expenses associated with being a public company and costs incurred to seek collaborations with respect to any of our product candidates.

Interest Income and Interest Expense

Interest income consists of interest earned on our cash and cash equivalents and short-term investments. Interest expense consists of interest incurred to finance equipment, office furniture and fixtures.

Critical Accounting Policies and Significant Judgments and Estimates
Our management's discussion and analysis of our financial condition and results of operations is based on our financial statements, which we have prepared in accordance with U.S. generally accepted accounting principles. The preparation of these financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the financial statements, as well as the reported revenues and expenses during the reporting periods. On an ongoing basis, we evaluate our estimates and judgments, including those described in greater detail below. We base our estimates on historical experience and on various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions.

While our significant accounting policies are more fully described in Note 2 to our financial statements appearing at the end of this prospectus, we believe that the following accounting policies are the most critical to aid you in fully understanding and evaluating our financial condition and results of operations.

Revenue Recognition

We recognize grant revenues as we receive the funding or when preclinical, clinical or regulatory milestones are met. Grant revenues are not refundable.

As described above, our collaboration agreements contain multiple elements, including non-refundable up-front license fees, research payments for ongoing research and development, payments associated with achieving development and regulatory milestones and royalties to be paid based on specified percentages of net product sales, if any. We consider a variety of factors in determining the appropriate method of revenue recognition under these arrangements, such as whether the elements are separable, whether there are determinable fair values and whether there is a unique earnings process associated with a particular element of an agreement.

We recognize revenue from non-refundable, up-front fees ratably over the term of our performance under the agreements. These payments are recorded as deferred revenue pending recognition. We recognize revenue related to research payments for ongoing research and development as the services are performed. Generally, the payments received are not refundable and are based on contractual

cost per full-time equivalent employee working on the project. We have not yet received any payments associated with achieving development and regulatory milestones, nor have we yet received royalties on net product sales.

Accrued Expenses

As part of the process of preparing our financial statements, we are required to estimate accrued expenses. This process involves communicating with our applicable personnel to identify services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of actual cost. The majority of our service providers invoice us monthly in arrears for services performed. We make estimates of our accrued





expenses as of each balance sheet date in our financial statements based on facts and circumstances known to us. Examples of estimated accrued expenses include:

- fees paid to contract research organizations in connection with preclinical and toxicology studies and clinical trials;
- fees paid to investigative sites in connection with clinical trials;
- fees paid to contract manufacturers in connection with the production of clinical trial materials; and
- professional service fees.

**Stock-Based Compensation**

Through December 31, 2005, in accordance with Statement of Financial Accounting Standards, or SFAS, No. 123, Accounting for Stock-Based Compensation, we elected to account for stock-based employee compensation using the intrinsic-value method under Accounting Principles Board, or APB, Opinion No. 25, Accounting for Stock Issued to Employees, and related interpretations. As such, we did not record expense on employee stock options granted when the exercise price of the options was equal to the fair value of the underlying stock on the date of the grant. Pro forma information regarding net loss and loss per share is required by SFAS No. 123 and has been determined as if we had accounted for employee stock option grants under the fair value method prescribed by that statement. Information with regard to the number of options granted, market price of the grants, vesting requirements and the maximum term of the options granted appears in Note 2 to our financial statements. Stock-based payments to non-employees are measured at the fair value of the stock-based instruments issued or the fair value of the goods or services received, whichever is more readily determinable.

For stock-based payments to both employees and non-employees, the fair value of the stock is a significant factor in determining credits or charges to operations. Because, prior to this offering, our shares have not been publicly traded, we must estimate the fair value of our common stock. There is no certainty that the results of our estimation would be the value at which the shares would be traded for cash. Factors that we consider in determining the fair value of our common stock include:

- pricing of private sales of our preferred stock;
- prior valuations of stock grants and preferred stock sales and the effect of events, including the progression of our product candidates, that have occurred between the time of the grants or sales;
- comparative rights and preferences of the security being granted compared to the rights and preferences of our other outstanding equity;
- comparative values of public companies discounted for the risk and limited

liquidity provided for in the shares we are issuing;

- perspective provided by unrelated valuation specialists;

- perspective provided by investment banks, including the likelihood of an initial public offering and our potential value in an initial public offering; and

- general economic trends.

Our board of directors has historically determined the fair value of our equity instruments, excluding preferred stock, based upon information available to it on the measurement dates. In connection with our grant of stock options in February 2005 and in February 2006, we performed a concurrent analysis to determine the fair market value of our common stock. We performed our analysis in accordance with applicable elements of the practice aid issued by the American Institute of Certified Public Accountants entitled Valuation of Privately Held Company Equity Securities Issued as Compensation. We used two primary valuation methodologies within the income approach to determine our enterprise valuation. First, we used a probability-weighted income approach that reduced our estimated cash flows based on the probability of successfully completing clinical trials. Second, we employed a traditional income approach that analyzed our manage-





ment's internal operating forecast without directly adjusting cash flows for the probability of success. We then weighted the probability-weighted income approach and the traditional income approach equally to arrive at a single enterprise value. Finally, we used that enterprise value in an option-pricing model to calculate the value of our outstanding common stock.

In December 2004, the Financial Accounting Standards Board, or FASB, issued SFAS No. 123(R), Share-Based Payment. SFAS No. 123(R) supersedes SFAS No. 123, APB Opinion No. 25 and its related implementation guidance. SFAS No. 123(R) will require compensation costs related to share-based payment transactions to be recognized in our financial statements. We will measure the amount of compensation cost based on the grant-date fair value of the equity or liability instruments issued. We will recognize compensation cost over the period that an employee provides service in exchange for the award. SFAS No. 123(R) is effective as of the beginning of the first interim or annual reporting period that begins after December 15, 2005. We cannot predict the full impact of adoption of SFAS No. 123(R) because it will depend on levels of share-based payments that we grant in the future. We have not yet determined the impact that implementing SFAS No. 123(R) will have on our results of operations or financial condition.

Income Taxes

As part of the process of preparing our financial statements, we are required to estimate our income taxes in each of the jurisdictions in which we operate. This process involves estimating our actual current tax exposure together with assessing temporary differences resulting from differing treatments of items for tax and accounting purposes. These differences result in deferred tax assets and liabilities. As of December 31, 2005, we had federal net operating loss carryforwards of $52.5 million, which expire starting in 2018, and federal research and development credit carryforwards of $3.7 million. We also had state net operating loss carryforwards of $49.7 million, which expire starting in 2009, and state research and development credit carryforwards of $2.8 million. At December 31, 2005, we recorded a full valuation allowance against our net deferred tax asset of approximately $45.5 million, as our management believes it cannot at this time conclude that it is more likely than not they will be realized. If we determine in the future that we will be able to realize all or a portion of our net deferred tax asset, an adjustment to the deferred tax valuation allowance would increase net income in the period in which we make such a determination. The Tax Reform Act of 1986 contains provisions that may limit the utilization of net operating loss credit carryforwards available to be used in any given year in the event of a change in ownership.

Results of Operations

Year Ended December 31, 2005 Compared to Year Ended December 31, 2004

Revenues. Revenues were $5.0 million in 2005, an increase of $3.4 million from revenues of $1.6 million in 2004. The increase resulted primarily from a significant increase in the number of grants and the dollar value of the grants that we received in 2005. In particular, in 2005 we received grants totaling $2.7 million from two patient advocacy groups, Cystic Fibrosis Foundation Therapeutics, Inc. and the Muscular Dystrophy Association, related to the clinical development of PTC124. We continue to seek additional grant revenue opportunities.

Research and Development Expense. Research and development expense was $21.1 million in 2005, an increase of $1.0 million, or 5.2%, from $20.1 million in 2004. The increase resulted primarily from the following changes in costs:

- increased costs for preclinical studies and manufacturing for PTC299 of $1.6 million;

- increased costs for preclinical studies for PTC124 of $895,000; and

- decreased costs for clinical studies and manufacturing for PTC124 of $1.6 million.

We expect that research and development expenses will increase in the future as a result of increased manufacturing and clinical development costs primarily relating to our PTC124 and PTC299 clinical development programs. The timing and amount of these expenses will depend upon the outcome of our





ongoing clinical trials, particularly the costs associated with our ongoing Phase 2 clinical trials of PTC124 and our planned Phase 1a and Phase 1b clinical trials of PTC299. The timing and amount of these expenses will also depend on the costs associated with potential future clinical trials of our product candidates and the related expansion of our research and development organization, regulatory requirements, advancement of our preclinical programs and product candidate manufacturing costs.

General and Administrative Expense. General and administrative expense was $7.9 million in 2005, an increase of $1.9 million, or 31.9%, from $6.0 million in 2004. The increase resulted principally from the following:

- increased personnel costs of $1.1 million attributable to increased salaries as well as increased headcount in legal and human resources;

- increased consulting expense of $290,000 related to commercialization planning and information technology infrastructure; and

- increased patent-related expense of $528,000 related to filings for PTC124, PTC299 and compounds in our HCV program.

We expect that general and administrative expense will increase in 2006 and in future periods as a result of increased payroll, expanded infrastructure, increased consulting, legal, accounting and investor relations expenses associated with being a public company, costs incurred to seek collaborations with respect to any of our product candidates and the stock-based compensation expense that we expect to record under SFAS No. 123(R).

Interest Income and Interest Expense. Interest income was $854,000 in 2005, compared to $579,000 in 2004. Interest expense was $141,000 in 2005, compared to $184,000 in 2004. The increase in interest income resulted from higher average interest rates in 2005, partially offset by lower average cash and cash equivalents and short-term investment balances during the year. The reduction in interest expense resulted from a reduction in our equipment financing and capital lease obligations during 2005.

Tax Benefit. We recognize tax benefits related to our sale of net operating losses in the New Jersey Tax Transfer Program. Our tax benefit was $479,000 in 2005 and $451,000 in 2004.

Year Ended December 31, 2004 Compared to Year Ended December 31, 2003

Revenues. Revenues were $1.6 million in 2004 and $756,000 in 2003. The increase resulted from an increase in the number of grants that we received in 2004.

Research and Development Expense. Research and development expense was $20.1 million in 2004, an increase of $2.4 million, or 13.4%, from $17.7 million in 2003. The increase resulted principally from the following:

- increased costs of clinical studies and manufacturing for PTC124 of $2.6 million;
- increased laboratory supply and library compound costs of $408,000;
- increased personnel costs of $1.1 million; and
- decreased in-process research and development of $1.4 million.

General and Administrative Expense. General and administrative expense was $6.0 million in 2004, an increase of $1.3 million, or 28.3%, from $4.7 million in 2003. The increase resulted principally from the following:

- increased personnel costs of $450,000 attributable to increased salaries and increased headcount in investor relations and general management;
- increased consulting expense of $419,000 related to increased legal and human resource temporary staffing;





- increased patent and legal expense of $254,000 related to filings for PTC124 and general corporate legal expenses; and
- increased miscellaneous corporate expenses of $216,000.

Interest Income and Interest Expense. Interest income was $579,000 in 2004, compared to $317,000 in 2003. Interest expense was $184,000 in 2004, compared to $358,000 in 2003. The increase in interest income resulted from higher average interest rates in 2004 and higher average cash and cash equivalents and short-term investment balances during the year. The reduction in interest expense resulted from a reduction in our equipment financing and capital lease obligations during 2004.

Tax Benefit. Our tax benefit related to our sale of net operating losses in the New Jersey Tax Transfer Program was $451,000 in 2004 and $235,000 in 2003.

Liquidity and Capital Resources

Sources of Liquidity

As a result of our significant research and development expenditures and the lack of any approved products to generate product sales revenue, we have not been profitable and have generated operating losses since we were incorporated in 1998. As such, we have funded our research and development operations primarily through sales of our preferred stock. Through December 31, 2005, we had received aggregate net proceeds of $128.5 million from these sales. We have also received funding from grant and foundation support, capital lease financings and interest earned on investments.

As of December 31, 2005, we had cash and cash equivalents and short-term investments of $37.8 million. We hold our cash and investment balances in a variety of interest-bearing instruments, including obligations of U.S. government agencies and money market accounts. We invest cash in excess of our immediate requirements with regard to liquidity and capital preservation. Wherever possible, we seek to minimize the potential effects of concentration and degrees of risk.

Cash Flows

The following table provides information regarding our cash flows and our capital expenditures for the years ended December 31, 2003, 2004 and 2005.

Year Ended December 31,

| 2003 | 2004 | 2005 |
|---|---|---|

(in thousands)

| | | | |
|---|---|---|---|
| Cash provided by (used in): | | | |
| Operating activities | $ (16,225 ) | $ (22,408 ) | $ (20,720 ) |
| Investing activities | 13,618 | (20,218 ) | (1,647 ) |
| Financing activities | 32,223 | 13,425 | 26,555 |
| Capital expenditures (included in investing activities above) | 667 | 1,121 | 963 |

Net cash used in operating activities was $20.7 million for the year ended December 31, 2005, $22.4 million for the year ended December 31, 2004 and $16.2 million in the year ended December 31, 2003. The net cash used in each of these periods primarily reflects the net loss for those periods, offset in part by depreciation, and changes in operating assets and liabilities.

Net cash used in investing activities was $1.6 million for the year ended December 31, 2005 and $20.2 million for the year ended December 31, 2004. Net cash provided by investing activities was $13.6 million for the year ended December 31, 2003. Cash used in investing activities was primarily related to net purchases of investments, and to a lesser extent, purchases of property and equipment.

Net cash provided by financing activities was $26.6 million for the year ended December 31, 2005, $13.4 million for the year ended December 31, 2004 and $32.2 million for the year ended December 31, 2003. Net cash provided by financing activities in 2005 was primarily attributable to the $26.5 million in proceeds





that we received from our Series E-2 preferred stock financing, and to a lesser extent, proceeds of $1.4 million in debt financing used to acquire property and equipment. Partially offsetting these proceeds were payments on debt obligations of $1.2 million. Net cash provided by financing activities in 2004 was primarily attributable to the subsequent closings on our Series E preferred stock financing, which initially closed in December 2003, totaling $14.9 million. Partially offsetting these proceeds were payments on debt obligations of $1.9 million. Net cash provided by financing activities in 2003 was primarily attributable to the initial closing of our Series E preferred stock financing totaling $34.2 million. Partially offsetting these proceeds were payments on debt obligations of $2.0 million.

Funding Requirements

We believe that the net proceeds from this offering, together with our existing cash and cash equivalents and short-term investments and research funding that we expect to receive under our collaborations, will be sufficient to enable us to fund our operating expenses and capital expenditure requirements until . We have based this estimate on assumptions that may prove to be wrong, and we could use our available capital resources sooner than we currently expect. Because of the numerous risks and uncertainties associated with the development and commercialization of our product candidates, and the extent to which we enter into collaborations with third parties to participate in their development and commercialization, we are unable to estimate the amounts of increased capital outlays and operating expenditures associated with our current and anticipated clinical trials. Our future capital requirements will depend on many factors, including:

- the progress and results of our clinical trials of PTC124 and PTC299;
- the success of our hepatitis C virus collaboration with Schering-Plough;
- the scope, progress, results and costs of preclinical development and laboratory testing and clinical trials for our other product candidates;
- the costs, timing and outcome of regulatory review of our product candidates;
- the number and development requirements of other product candidates that we pursue;

- the costs of commercialization activities, including product marketing, sales and distribution;

- the costs of preparing, filing and prosecuting patent applications and maintaining, enforcing and defending intellectual property-related claims;

- the extent to which we acquire or invest in businesses, products and technologies; and

- our ability to establish and maintain collaborations.

We do not anticipate that we will generate product revenue for at least the next several years. In the absence of additional funding, we expect our continuing operating losses to result in increases in our cash used in operations over the next several quarters and years. To the extent our capital resources are insufficient to meet our future capital requirements, we will need to finance our future cash needs through public or private equity offerings, debt financings or corporate collaboration and licensing arrangements. Except for research funding by our collaborators, particularly Schering-Plough, we do not currently have any commitments for future external funding.

Additional equity or debt financing, grants, or corporate collaboration and licensing arrangements, may not be available on acceptable terms, if at all. If adequate funds are not available, we may be required to delay, reduce the scope of or eliminate our research and development programs, reduce our planned commercialization efforts or obtain funds through arrangements with collaborators or others that may require us to relinquish rights to certain drug candidates that we might otherwise seek to develop or commercialize independently. In addition, any future equity funding may dilute the ownership of our equity investors.



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Contractual Obligations

The following table summarizes our significant contractual obligations and commercial commitments as of December 31, 2005 (in thousands).

| | Total | Less than 1 Year | 1-3 Years | 4-5 Years | More than 5 Years | |
|---|---|---|---|---|---|---|
| Equipment financing obligations | $ 1,282 | $ 478 | $ 774 | $ 30 | - | |
| Operating lease obligations | 1,338 | 384 | 785 | 169 | - | |
| Total fixed contractual obligations | $ 2,620 | $ 862 | $ 1,559 | $ 199 | - | |

Quantitative and Qualitative Disclosures About Market Risk
The primary objective of our investment activities is to preserve our capital to fund operations. We also seek to maximize income from our investments without assuming significant risk. To achieve our objectives, we maintain a portfolio of cash equivalents and investments in a variety of securities of high credit quality. As of December 31, 2005, we had cash and cash equivalents and short-term investments of $37.8 million. A portion of our investments may be subject to interest rate risk and could fall in value if market interest rates increase. However, because our investments are short-term in duration, we believe that our exposure to interest rate risk is not significant and a 1% movement in market interest rates would not have a significant impact on the total value of our portfolio. We actively monitor changes in interest rates.
Recent Accounting Pronouncements

In December 2004, the FASB issued SFAS No. 123(R). SFAS No. 123(R) supersedes SFAS No. 123, APB Opinion No. 25 and its related implementation guidance. SFAS No. 123(R) will require compensation costs related to share-based payment transactions to be recognized in the financial statements. The amount of compensation cost will be measured based on the grant-date fair value of the equity or liability instruments issued. Compensation cost will be recognized over the period that an employee provides service in exchange for the award. SFAS No. 123(R) is effective as of the beginning of the first interim or annual reporting period that begins after December 15, 2005. We cannot predict the full impact of adoption of SFAS No. 123(R) at this time because it will depend on

levels of share-based payments granted in the future. We have not yet determined the impact that implementing SFAS No. 123(R) will have on our results of operations or financial condition.

In June 2005, the FASB issued SFAS No. 154, Accounting Changes and Error Corrections. This statement requires that a voluntary change in accounting principle be applied retrospectively with all prior period financial statements presented on the basis of the new accounting principle, unless it is impracticable to do so. SFAS No. 154 also provides that (1) a change in method of depreciating or amortizing a long-lived nonfinancial asset be accounted for as a change in estimate (prospectively) that was effected by a change in accounting principle, and (2) correction of errors in previously issued financial statements should be termed a "restatement." The new standard is effective for accounting changes and correction of errors made in fiscal years beginning after December 15, 2005. Early adoption of this standard is permitted for accounting changes and correction of errors made in fiscal years beginning after June 1, 2005. We do not anticipate that the adoption of this statement will have a material impact on our results of operations or financial condition.

In November 2005, the FASB issued FASB Staff Position FAS 115-1 and FAS 124-1, The Meaning of Other-Than-Temporary Impairment and Its Application to Certain Investments. This Staff Position addresses





the determination as to when an investment is considered impaired, whether that impairment is other than temporary and the measurement of an impairment loss. This Staff Position also includes accounting considerations subsequent to the recognition of an other-than-temporary impairment and requires certain disclosures about unrealized losses that have not been recognized as other-than-temporary impairments. The guidance in the Staff Position is required to be applied to reporting periods beginning after December 15, 2005. We will adopt the provisions of this Staff Position in 2006 and do not currently believe that implementation will have a material effect on our results of operations or financial condition.

# EXHIBIT 7

PRINTER-FRIENDLY

**SUPER SEARCH**
Advanced search for assistance

**BY RECIPIENT**
Search by name: GO
Top 100 Recipients (2006)
By type of recipient
By recipient state
By recipient cong. district

**BY PLACE OF PERFORMANCE**
Overview by state

**BY AGENCY**
Overview by major agency

**BY ASSISTANCE TYPE**
Overview by type of assistance

**BY PROGRAM**
By program

The assistance database is compiled from government data last released on 08/28/2007

Made possible with the support of The Sunlight Foundation

# Assistance to PTC THERAPEUTICS INC in NJ (FY 2000-2006)

(MAP IT)

Search Criteria Used (More)

| | | |
|---|---|---|
| Federal Fiscal Year | ALL | GO |
| Level of Detail | Summary | GO |
| Type of Report Output | HTML | GO |

## Summary

Federal dollars: **$8,321,548**
Total number of recipients: **1**
Total number of transactions: **20**
Get list of recipients
Get list of transactions

## Top 5 Known Congressional Districts where Recipients are Located

| | |
|---|---|
| Invalid district: | $0 |

## Top 10 Recipients

| | |
|---|---|
| PTC THERAPEUTICS INC | $8,321,548 |

## Recipient Type

| | |
|---|---|
| For Profits | $7,706,808 |
| Nonprofits | $614,740 |
| Other | $0 |
| Higher Education | $0 |
| Government | $0 |
| Individuals | $0 |

## Assistance Type

| | |
|---|---|
| Grants and Cooperative Agreements | $8,321,548 |
| Other | $0 |
| Loans (both direct and guaranteed) | $0 |
| Insurance | $0 |
| Direct Payments (both specified and | $0 |

## Top 5 Programs

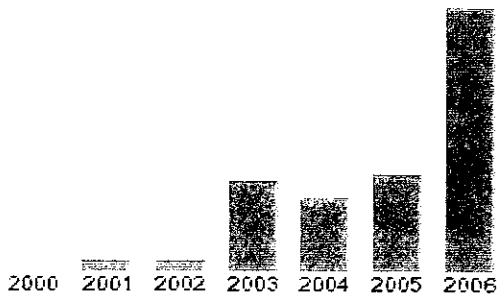
| | |
|---|---|
| 12.420: Military Medical Research and Development | $2,834,155 |
| 93.856: Microbiology and Infectious Diseases Research | $2,444,297 |
| 93.395: Cancer Treatment Research | $1,647,757 |
| 93.103: Food and Drug Administration_Research | $757,623 |
| 93.865: Child Health and Human Development Extramural Research | $465,186 |

Expand summary to all programs

## Top 5 Agencies Providing Assistance

| | |
|---|---|
| HHS - National Institutes of Health | $4,729,770 |
| ARMY, Department of the (except Corps of Engineers Civil Program) | $2,834,155 |
| HHS - Food and Drug Administration | $757,623 |

## Trend




| | |
|---|---|
| 2000 | $0 |
| 2001 | $140,000 |
| 2002 | $126,560 |
| 2003 | $1,370,936 |
| 2004 | $1,130,779 |
| 2005 | $1,471,417 |
| 2006 | $4,081,856 |

unrestricted)

Expand all summaries to all values, not just top 5 or 10

*END OF REPORT*

This search was done on May 4, 2008.

(MAP IT)

Search Criteria Used

| | | |
|---|---|---|
| Federal Fiscal Year | ALL | GO |
| Assigned Recipient ID | 715568 | |
| Sort By | No sort (summary only) | |
| Level of Detail | Summary | GO |
| Type of Report Output | HTML | GO |

The assistance database is compiled from government data last released on 08/28/2007

This search result was produced as a project of OMB Watch. The data was obtained from the U.S. Census Bureau's Federal Assistance Award Data System (FAADS).

# EXHIBIT 8

# Phase 2b Study of PTC124 in Duchenne/Becker Muscular Dystrophy (DMD/BMD)

**This study is currently recruiting participants.**

Information provided by PTC Therapeutics

**This Tabular View shows the required WHO registration data elements as marked by †**

## Descriptive Information Fields

| | |
|---|---|
| **Brief Title †** | Phase 2b Study of **PTC124** in Duchenne/Becker Muscular Dystrophy (DMD/BMD) |
| **Official Title †** | A Phase 2b Efficacy and Safety Study of **PTC124** in Subjects With Nonsense-Mutation-Mediated Duchenne Muscular Dystrophy and Becker Muscular Dystrophy |
| **Brief Summary** | Duchenne/Becker muscular dystrophy (DMD/BMD) is a genetic disorder that develops in boys. It is caused by a mutation in the gene for dystrophin, a protein that is important for maintaining normal muscle structure and function. Loss of dystrophin causes muscle fragility that leads to weakness and loss of walking ability during childhood and teenage years. A specific type of mutation, called a nonsense (premature stop codon) mutation is the cause of DMD/BMD in approximately 10-15% of boys with the disease. **PTC124** is an orally delivered, investigational drug that has the potential to overcome the effects of the nonsense mutation. This study is a Phase 2b trial that will evaluate the clinical benefit of **PTC124** in boys with DMD/BMD due to a nonsense mutation. The main goals of the study are to understand whether **PTC124** can improve walking, activity, muscle function, and strength and whether the drug can safely be given for a long period of time. |
| **Detailed Description** | This study is a Phase 2b, multicenter, randomized, double-blind, placebo-controlled, dose-ranging, efficacy and safety study, designed to document the clinical benefit of PTC124 when administered as therapy of patients with DMD/BMD due to a nonsense mutation (premature stop codon) in the dystrophin gene. It is planned that ~165 boys who are at least 5 years of age and can walk at least 75 meters (80 yards) will be enrolled. Study subjects will be enrolled at sites in North America, Europe, Israel, and Australia. They will be randomized in a 1:1:1 ratio to either a higher dose of PTC124, a lower dose of PTC124, or placebo. Subjects will receive study drug 3 times per day (at breakfast, lunch, and dinner) for 48 weeks. Subjects will be evaluated at clinic visits every 6 weeks. Additional safety laboratory testing, which may be performed at the investigational site or at an accredited local laboratory or clinic, is required every 3 weeks for the first 24 weeks of the study. At the completion of blinded treatment, all compliant participants will be eligible to receive open-label PTC124 in a separate extension study. |
| **Study Phase** | Phase II, Phase III |

| | |
|---|---|
| **Study Type †** | Interventional |
| **Study Design †** | Treatment, Randomized, Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor), Placebo Control, Parallel Assignment, Safety/Efficacy Study |
| **Primary Outcome Measure †** | To determine the effect of **PTC124** on ambulation in subjects with nonsense-mutation-mediated DMD/BMD (as assessed by changes in the distance walked during a 6-minute walk test) [ Time Frame: 12 months ] [ Designated as safety issue: No ] |
| **Secondary Outcome Measure †** | Activity in the community setting [ Time Frame: 12 months ] [ Designated as safety issue: No ]<br>Proximal muscle function [ Time Frame: 12 months ] [ Designated as safety issue: No ]<br>Muscle strength [ Time Frame: 12 months ] [ Designated as safety issue: No ]<br>Muscle fragility [ Time Frame: 12 months ] [ Designated as safety issue: No ]<br>Biceps muscle dystrophin expression [ Time Frame: 12 months ] [ Designated as safety issue: No ]<br>Quality of Life [ Time Frame: 12 months ] [ Designated as safety issue: No ]<br>Cognitive ability [ Time Frame: 12 months ] [ Designated as safety issue: No ]<br>Cardiac function [ Time Frame: 12 months ] [ Designated as safety issue: No ]<br>Frequency of accidental falls during ambulation [ Time Frame: 12 Months ] [ Designated as safety issue: No ]<br>Treatment satisfaction [ Time Frame: 12 Months ] [ Designated as safety issue: No ]<br>Safety [ Time Frame: 12 months ] [ Designated as safety issue: Yes ]<br>Compliance with treatment [ Time Frame: 12 months ] [ Designated as safety issue: No ]<br>**PTC124** pharmacokinetics [ Time Frame: 12 months ] [ Designated as safety issue: No ] |
| **Condition †** | Duchenne Muscular Dystrophy<br>Becker Muscular Dystrophy |
| **Intervention †** | Drug: **PTC124** |
| **MEDLINE PMIDs** | |
| **Links** | |

## Recruitment Information Fields

| | |
|---|---|
| **Recruitment Status †** | Recruiting |
| **Enrollment †** | 165 |
| **Start Date †** | February 2008 |
| **Completion Date** | August 2010 |
| **Eligibility Criteria †** | Inclusion Criteria:<br>• Ability to provide written informed consent (parental/guardian consent if applicable)/assent (if <18 years of age)<br>• Male sex.<br>• Age ≥5 years.<br>• Phenotypic evidence of DMD/BMD based on the onset of characteristic clinical symptoms or signs (ie., proximal muscle weakness, waddling gait, and Gowers' maneuver) by 9 years of age, an elevated serum creatinine kinase level, and ongoing difficulty with walking. |

- Documentation of the presence of a nonsense point mutation in the dystrophin gene as determined by gene sequencing from a laboratory certified by the College of American Pathologists (CAP), the Clinical Laboratory Improvement Act/Amendment (CLIA) or an equivalent organization.
- Ability to walk ≥75 meters unassisted during the screening 6-minute walk test.
- Documentation that a baseline renal ultrasound has been performed.
- Confirmed screening laboratory values within the central laboratory ranges (hemoglobin, adrenal, renal and serum electrolytes parameters)
- Willingness and ability to comply with scheduled visits, drug administration plan, study procedures, laboratory tests, and study restrictions.

Exclusion Criteria:

- Treatment with systemic aminoglycoside antibiotics within 3 months prior to start of study treatment.
- Initiation of systemic corticosteroid therapy within 6 months prior to start of study treatment or change in systemic corticosteroid therapy (eg, initiation, change in type of drug, dose modification not related to body weight change, schedule modification, interruption, discontinuation, or reinitiation) within 3 months prior to start of study treatment.
- Any change (initiation, change in type of drug, dose modification, schedule modification, interruption, discontinuation, or reinitiation) in prophylaxis/treatment for congestive heart failure within 3 months prior to start of study treatment.
- Treatment with warfarin within 1 month prior to start of study treatment.
- Prior therapy with PTC124.
- Known hypersensitivity to any of the ingredients or excipients of the study drug (Litesse® UltraTM [refined polydextrose], polyethylene glycol 3350, Lutrol® micro F127 [poloxamer 407], mannitol 25C, crospovidone XL10, hydroxyethyl cellulose, vanilla, Cab-O-Sil® M5P [colloidal silica], magnesium stearate).
- Exposure to another investigational drug within 2 months prior to start of study treatment.
- History of major surgical procedure within 30 days prior to start of study treatment.
- Ongoing immunosuppressive therapy (other than corticosteroids).
- Ongoing participation in any other therapeutic clinical trial.
- Expectation of major surgical procedure (eg, scoliosis surgery) during the 12 month treatment period of the study.
- Requirement for daytime ventilator assistance.
- Clinical symptoms and signs of congestive heart failure (American College of Cardiology/American Heart Association Stage C or Stage D) or evidence on echocardiogram of clinically significant myopathy
- Prior or ongoing medical condition (eg, concomitant illness, psychiatric condition, behavioral disorder, alcoholism, drug abuse), medical history, physical findings, electrocardiogram findings, or laboratory abnormality that, in the investigator's opinion, could adversely affect the safety of the subject, makes it unlikely that the course of treatment or follow-up would be completed, or could impair the assessment of study results.

| | |
|---|---|
| **Gender** | Male |
| **Ages** | 5 Years and older |
| **Accepts Healthy Volunteers** | No |

| | |
|---|---|
| **Contacts** †† | Contact: Diane Goetz 908-912-9256 dgoetz@ptcbio.com |
| **Location Countries** † | United States, Australia, Belgium, Canada, France, Germany, Israel, Italy, Spain, Sweden, United Kingdom |

## Administrative Information Fields

| | |
|---|---|
| **NCT ID** † | NCT00592553 |
| **Organization ID** | **PTC124**-GD-007-DMD |
| **Secondary IDs** †† | |
| **Study Sponsor** † | PTC Therapeutics |
| **Collaborators** †† | |
| **Investigators** † | |
| **Information Provided By** | PTC Therapeutics |
| **Verification Date** | July 2008 |
| **First Received Date** † | January 1, 2008 |
| **Last Updated Date** | July 8, 2008 |

† **Required WHO trial registration data element.**
†† **WHO trial registration data element that is required only if it exists.**