FAA defining the low cycle fatigue life of GE 90 rotating components. The analysis included an updated material property data base and other refinements that resulted in a reduction of the published low cycle fatigue retirement life limit for certain rotating components. The FAA has determined that this AD is necessary to mandate reduced life limits for certain rotating components installed in GE90–76B engines. If not corrected, this condition could result in a low cycle fatigue failure of a rotating component and possibly an uncontained engine failure.

The FAA has reviewed and approved the technical contents of General Electric Company GE90 Alert Service Bulletin (ASB) No. 72–A318, dated June 27, 1997, that describes reduced life limits for certain rotating components. Since an unsafe condition has been identified that is likely to exist or develop on other products of this same type design, the proposed AD would require reduced life limits for certain rotating components. The actions would be required to be accomplished in accordance with the ASB described previously.

There are approximately twenty-five engines of the affected design in the worldwide fleet. The manufacturer has advised the FAA that there are currently no engines installed on aircraft of U.S. registry that would be affected by this proposed AD. Therefore, there is no associated cost impact on U.S. operators as a result of this proposed AD.

The FAA estimates that the most representative engines would have four of the seven life-limited-reduced components installed. Assuming the four components are the High Pressure Compressor Rotor (HPCR) 2–6 spool, HPCR stage 7 disk, HPCR CDP seal and the Low Pressure Turbine cone shaft and that the parts cost is proportional to the reduction of the low cycle fatigue retirement lives, the required parts would cost approximately $189,123 per engine. Based on these figures, the FAA estimates the total cost impact of this proposed AD would be $189,123 per engine.

The regulations proposed herein would not 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. Therefore, in accordance with Executive Order 12612, it is determined that this proposal would not have sufficient federalism implications to warrant the preparation of a Federalism Assessment.

For the reasons discussed above, I certify that this proposed regulation: (1) Is not a ''significant regulatory action'' under Executive Order 12866; (2) is not a ''significant rule'' under the DOT Regulatory Policies and Procedures (44 FR 11034, February 26, 1979); and (3) if promulgated, will not have a significant economic impact, positive or negative, on a substantial number of small entities under the criteria of the Regulatory Flexibility Act. A copy of the draft regulatory evaluation prepared for this action is contained in the rules docket. A copy of it may be obtained by contacting the rules docket at the location provided under the caption **ADDRESSES**.

### List of Subjects in 14 CFR Part 39

Air transportation, Aircraft, Aviation safety, Safety.

### The Proposed Amendment

Accordingly, pursuant to the authority delegated to me by the Administrator, the Federal Aviation Administration proposes to amend part 39 of the Federal Aviation Regulations (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. Section 39.13 is amended by adding the following new airworthiness directive:

**General Electric Company:** Docket No. 97–ANE–28–AD.

*Applicability:* General Electric Company (GE) GE90–76B model turbofan engines installed on but not limited to Boeing 777 aircraft.

**Note 1:** This airworthiness directive (AD) applies to each engine identified in the preceding applicability provision, regardless of whether it has been modified, altered, or repaired in the area subject to the requirements of this AD. For engines that have been modified, altered, or repaired so that the performance of the requirements of this AD is affected, the owner/operator must request approval for an alternative method of compliance in accordance with paragraph (c) of this AD. The request should include an assessment of the effect of the modification, alteration, or repair on the unsafe condition addressed by this AD; and, if the unsafe condition has not been eliminated, the request should include specific proposed actions to address it.

*Compliance:* Required as indicated, unless accomplished previously.

To prevent a low cycle fatigue failure of a rotating component and possibly an uncontained engine failure, accomplish the following:

(a) Remove from service those components listed in Table 1 of GE Alert Service Bulletin (ASB) No. 72–A318, dated June 27, 1997, and replace with a serviceable component, prior to exceeding the new cyclic life limits established in paragraph (d) of ASB No. 72–A318, dated June 27, 1997.

**Note 2:** These revised component life limits will be added to the GE90 Engine Manual, Chapter 05–11–00, Life Limits 001 in the August 1, 1997, Revision.

(b) Except as provided in paragraph (c) of this AD, no replacement times may be approved for these parts.

(c) An alternative method of compliance or adjustment of the compliance time that provides an acceptable level of safety may be used if approved by the Manager, Engine Certification Office. Operators shall submit their requests through an appropriate FAA Principal Maintenance Inspector, who may add comments and then send it to the Manager, Engine Certification Office.

**Note 3:** Information concerning the existence of approved alternative methods of compliance with this airworthiness directive, if any, may be obtained from the Engine Certification Office.

(d) Special flight permits may be issued in accordance with sections 21.197 and 21.199 of the Federal Aviation Regulations (14 CFR 21.197 and 21.199) to operate the aircraft to a location where the requirements of this AD can be accomplished.

Issued in Burlington, Massachusetts, on September 18, 1997.

**Mark C. Fulmer,**

*Acting Manager, Engine and Propeller Directorate, Aircraft Certification Service.*

[FR Doc. 97–25312 Filed 9–23–97; 8:45 am]

**BILLING CODE 4910–13–U**

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

## Food and Drug Administration

## 21 CFR Part 312

**[Docket No. 97N–0030]**

## Investigational New Drug Applications; Proposed Amendment to Clinical Hold Regulations for Products Intended for Life-Threatening Diseases

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

**ACTION:** Proposed rule.

**SUMMARY:** The Food and Drug Administration (FDA) is proposing to amend the provisions of its regulations governing investigational new drug applications (IND's) to permit FDA to place a clinical hold on one or more studies under an IND involving a drug that is intended to treat a life-threatening disease affecting both genders if men or women with reproductive potential who have the disease and are otherwise eligible but are excluded from participation in an

investigation only because of a risk or potential risk of reproductive or developmental toxicity from use of the investigational drug. Women have been excluded in the past from early clinical trials because of a risk or potential risk of reproductive or developmental toxicity. Therefore, the primary goal of this proposed amendment is to ensure that women with reproductive potential who have a life-threatening disease are not automatically excluded in the future for that reason. The proposed rule would not impose requirements to enroll or recruit a specific number of men or women with reproductive potential.

The proposal would implement a recommendation of both the National Task Force on AIDS Drug Development (the AIDS Task Force) and the Presidential Advisory Council on Human Immunodeficiency Virus/ Acquired Immune Deficiency Syndrome (HIV/AIDS).

**DATES:** Submit written comments by December 23, 1997. FDA proposes that any final rule that may issue based on this proposal become effective 60 days after its date of publication in the **Federal Register**.

**ADDRESSES:** Submit written comments to the Dockets Management Branch (HFA305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857.

**FOR FURTHER INFORMATION CONTACT:** Nancy E. Derr, Center for Drug Evaluation and Research (HFD–5), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–5400, FAX 301–594–6197.

**SUPPLEMENTARY INFORMATION:**

## I. Introduction

On January 19, 1995, the AIDS Task Force made a series of recommendations related to women's participation in the drug development process, including the recommendation that women with reproductive potential not be excluded from studies of drugs being tested for use against life-threatening diseases, particularly HIV- and AIDS-related diseases. This recommendation was based, in part, on data provided by the HIV Law Project of the AIDS Service Center (Ref. 1). The data demonstrated that participation of women in AIDS clinical drug trials was low.[1] In the view of members of the AIDS Task Force, this low rate of participation raised doubts as to whether a sufficient number of women were being included in these clinical trials to provide clinically meaningful information about the effects of HIV and AIDS drugs in the women who would be using them. These data also raised questions and concerns among women with HIV regarding their ability to participate in trials for promising new experimental therapies. On December 8, 1995, the Presidential Advisory Council on HIV/ AIDS adopted the AIDS Task Force's recommendation that FDA amend its regulations to prevent the exclusion of women who have a life-threatening disease from any phase of clinical investigations for that disease because of their reproductive potential. If adopted, this proposed rule would implement that recommendation.

FDA's policies regarding the participation of women in clinical investigations have evolved over time. The agency now believes it is important to codify its policies regarding the participation of women with reproductive potential in clinical investigations of drug products intended to treat life-threatening diseases. The proposed amendments to the clinical hold regulations address the exclusion from clinical trials of members of either gender who have a life-threatening disease. The primary intent, however, is to ensure that women who have a life-threatening disease are not automatically excluded from investigational trials of drug products for that disease due to a perceived risk or potential risk of reproductive or developmental toxicity from the use of the investigational drug. The proposal would not apply to clinical studies conducted: (1) Exclusively in healthy volunteers; (2) under special circumstances, such as studies of a single-gender population (e.g., studies evaluating the excretion of a drug in semen or its effects on menstrual function); or (3) in men, as long as a study that does not exclude subjects with reproductive potential has been planned or is being conducted in women. For the purposes of this rulemaking, FDA does not intend the phrase ''women with reproductive potential'' to include pregnant women. The agency acknowledges the need for more information on the safety and effectiveness of drugs and biological products in pregnant women and is continuing to explore this complex issue in other forums.

## II. Clinical Hold Regulations

A clinical hold is an order, under § 312.42 (21 CFR 312.42), that FDA may issue to a sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation for the development of a new drug, antibiotic drug, or biological product. A clinical hold may apply to one or more of the investigations under an IND. When FDA places a proposed study on clinical hold, subjects in that study may not be given the investigational drug. When FDA places an ongoing study on clinical hold, no new subjects may be recruited to the study and placed on the investigational drug; subjects already in the study should be taken off the therapy involving the investigational drug unless FDA specifically permits continuation of the therapy in the interest of patient safety.

FDA may place a clinical hold on a proposed or ongoing phase 1, phase 2, or phase 3 investigation (§ § 312.42(b)(1) and (b)(2)), a proposed or ongoing treatment IND or treatment protocol (§ 312.42(b)(3)), or any investigation that is not designed to be adequate and well controlled (§ 312.42(b)(4)). Generally, FDA will attempt to discuss and resolve the matter with the sponsor before issuing a clinical hold order unless subjects are exposed to immediate and serious risk (§ 312.42(c)). When the deficiency that prompts a clinical hold is corrected by the sponsor, the investigation generally may resume (§ 312.42(e)).

## III. Evolution of FDA Policy Regarding Participation of Women in Clinical Investigations

Although the proposed amendments to the clinical hold regulations address the exclusion from trials for drug products to treat a life-threatening disease of members of either gender who have the disease, the primary intent of the proposed amendments is to ensure that women who have a life-threatening disease are not excluded from clinical trials solely because of their reproductive potential. Since 1977, when FDA first issued guidance on the participation of women in clinical trials, women with reproductive potential often have been excluded from early clinical trials due to the perceived risk or potential risk of reproductive or developmental toxicity. As the following discussion shows, however, views on the participation of women, as well as corresponding FDA guidance and regulations pertaining to clinical trials of investigational drugs, reflect a

[1] As of January 1992, 14,799 participants were enrolled in U.S. AIDS Clinical Trial Group studies sponsored by the National Institute of Allergy and Infectious Diseases, of whom only 1,151 were adult women. (Pearl, M., et al., ''Women in U.S. Government Clinical Trials,'' VIII International Conference on AIDS, 8(2: B235, 1992.)

In 1993, 21,598 participants were enrolled, while only 1,952 were adult women. (Korvick, J.A., ''Trends in Federally Sponsored Clinical Trials,'' in *Until the Cure: Caring for Women With HIV*, A. Kurth, editor, pp. 94–103, 1993).

significant evolution of thought during the past two decades within the agency and the scientific community. In addition, during this period considerable public attention has been paid to questions about the participation of women in general in clinical trials. The following background information highlights key FDA statements on the inclusion of women, especially women with reproductive potential, in the clinical drug testing process. Throughout, the phrase ''reproductive toxicity'' refers to toxicities to reproductive organs, while the term ''developmental toxicity'' refers to toxicities to potential offspring.

The agency first provided formal guidance on the participation of women with reproductive potential in clinical trials in a 1977 guideline entitled ''General Considerations for the Clinical Evaluation of Drugs'' (the 1977 guideline). Developed within the protective environment brought on by the thalidomide experience a decade earlier, the 1977 guideline stated that women of childbearing potential should not be included in phase 1 and early phase 2 trials because of the potential for reproductive or developmental toxicity. Women with childbearing potential could be included in later phase 2 and phase 3 studies, as long as animal teratogenicity and the female part of animal fertility studies had been completed and there was some evidence of effectiveness from earlier studies. The 1977 guideline made an exception to this recommendation for early trials involving drug products intended to treat life-threatening diseases, even in the absence of adequate reproduction studies in animals. Despite this exception, however, the exclusion of women of reproductive potential from early trials was in some cases applied to trials for drug products to treat life-threatening diseases.

Since the 1977 guideline was issued, views have evolved about the participation of women in clinical trials. Views also have evolved about informed individuals assuming the risks of investigational products. Recognition has increased in the agency and among the public that patients, especially those with a life-threatening disease, are willing to accept considerable risks to participate in studies that may benefit them. There is increased public recognition of ethical issues such as fairness and an individual patient's ability to participate in decisions that involve personal risk. There is growing understanding that information about population subgroups, e.g., subsets grouped by age, gender, or race, is needed to evaluate the safety and effectiveness of therapies and to refine labeling, patient selection, and dose selection in those groups. Failure to obtain such information may limit the usefulness of a treatment or expose a segment of the population to risk. These perspectives have influenced FDA policy since the early 1980's.

In the **Federal Register** of July 22, 1993 (58 FR 39406), FDA issued a ''Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs'' (the 1993 guideline). That guideline revoked the 1977 guideline's recommendation regarding restrictions on the participation of women with reproductive potential in early clinical trials, including clinical pharmacology studies (e.g., dose tolerance, bioavailability, and mechanism of action studies) and early therapeutic studies. The 1993 guideline left the determination about whether the risks and benefits support the participation of women with reproductive potential to patients, investigators, sponsors, and institutional review boards (IRB's).

Although the 1993 guideline does not require participation of women in any particular trial, it sets forth FDA's general expectations regarding the inclusion of both women and men in drug development, analyses of clinical data by gender, assessment of potential pharmacokinetic differences between genders, and conduct of specific additional studies in women, where indicated. The 1993 guideline is consistent with an earlier guideline, issued in 1988 and entitled, ''Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications'' published in the **Federal Register** of October 7, 1988 (53 FR 39524), in which FDA advised that new drug applications (NDA's) should include analyses of data for population subsets, including age, gender, and race, to identify subgroup differences in effectiveness and adverse reactions to investigational drugs. The 1993 guideline notes that participants in clinical studies should, in general, reflect the population that will receive the drug once it is marketed and encourages the participation of women, whether or not they have a serious disease, in early phases of all clinical trials. It points out that including women early is particularly important when a drug is intended for a serious disease and may become available rapidly, for example, through distribution under a treatment IND (§§ 312.34 and 312.35 (21 CFR 312.34 and 312.35)), or marketing under subpart E of part 601 (21 CFR part 601) and consisting of §§ 601.40 through 601.46 or subpart H of part 314 (21 CFR part 314) and consisting of §§ 314.500 through 314.560. (See section IV.A. of this document for a description of these procedures.)

FDA has long recognized the importance of gender data in evaluating the safety and efficacy of a drug. This is reflected in other FDA guidances issued in 1993 (''New Drug Evaluation Guidance Document: Refusal to File'' and ''Center for Biologics Evaluation and Research (CBER): Refusal to File (RTF) Guidance for Product License Applications (PLA's) and Establishment License Applications (ELA's)'' (58 FR 38770, July 20, 1993). These documents state that FDA may refuse to file an application if it contains inadequate evaluation of the safety and/or effectiveness of a drug, biological therapeutic, or vaccine in specific populations, such as in women, intended to use the product.

FDA also recently proposed a rule that would codify expectations regarding presentation in NDA's of safety and effectiveness data by gender as described in the 1993 guideline. Although it would not require the inclusion of women with reproductive potential in clinical investigations, the rule would require the presentation in NDA's of certain data by specific population subgroups, including women, who are likely to receive the drug once it is marketed (60 FR 46794, September 8, 1995).

The 1977 guideline never recommended excluding women with reproductive potential from trials for drugs to treat life-threatening diseases. Moreover, the 1993 guideline recommended that the exclusion of such women be removed from all trials. Nevertheless, a recent limited agency review of clinical trial protocols dealing with antiviral drugs revealed that women with reproductive potential are still being excluded from some protocols of some investigational trials for drug products intended to treat HIV, a life-threatening disease. The agency believes that this violates ethical principles and in some cases could lead to inadequate data on use in women prior to wide availability of the drug. The agency has concluded that women with reproductive potential who have a life-threatening disease should no longer be excluded from investigational clinical trials for drug products to treat that disease because of a risk or potential risk of reproductive or developmental toxicity from use of the investigational drug, as long as patient volunteers are fully informed of the risks, in compliance with informed

consent regulations in part 50 (21 CFR part 50).

## IV. Rationale for the Proposed Rule

In the past, women with a life-threatening disease who have reproductive potential often have been excluded from early investigational clinical trials for that disease because of the potential risk of reproductive or developmental toxicity. As a result, although it applies to the exclusion of either gender, the primary goal of this proposed rule is to ensure that women who have a life-threatening disease are not excluded from investigational drug studies for that disease because of their reproductive potential.

In lengthy discussions with representatives of industry and the public during the development of this proposal (Ref. 2), the view was expressed that many early clinical studies involving life-threatening diseases offer the potential for therapeutic benefit. In some cases, for example, participation in an early clinical study is a prerequisite for enrollment in later studies. Based on these discussions, FDA has concluded that all trials involving patients with life-threatening diseases should, for purposes of this proposed rule, be considered to have therapeutic potential and that this proposal would apply to studies in any phase of a clinical investigation that enroll participants with a life-threatening disease.

In developing this proposal, FDA focused on four important factors: (1) FDA is committed to expanding access to and accelerating approval of new therapies for life-threatening diseases; (2) important ethical principles underlie the belief that neither gender should be excluded from early clinical trials involving a life-threatening disease because of their reproductive potential; (3) the mechanisms are in place, or are available, to protect individuals who participate in clinical trials from potential risks; and (4) FDA is committed to expanding the collection of gender-specific data on investigational therapies, especially for those populations who ultimately will be using the therapies. These four factors are discussed in detail in the following sections of this document.

### *A. Expanding Access and Accelerating Approval*

FDA is committed to expanded patient access to potentially beneficial therapies for life-threatening and serious diseases, such as cancer and AIDS, through the IND process. Mechanisms for expanding access include treatment IND's (§§ 312.34 and 312.35), parallel track protocols (57 FR 13250, April 15, 1992), and other open-label protocols either for groups of patients or for one patient. Tens of thousands of patients have received promising pharmaceuticals under expanded access mechanisms.

In many cases, the risk-benefit assessment for investigational drugs for life-threatening or even serious diseases differs from that for investigational drugs for treating diseases not considered life-threatening or serious. In establishing procedures for the investigation of drugs for life-threatening diseases, FDA has recognized that physicians and patients are generally willing to accept greater risks or side effects from these medical products than they would accept from products that treat less serious diseases (53 FR 41516 at 41518, October 21, 1988).

FDA also is committed to expediting the approval of investigational drugs for treatment of life-threatening and serious diseases. The agency has issued regulations for the expedited development of new therapies intended to treat persons with life-threatening or severely debilitating diseases (subpart E of part 312 (21 CFR part 312) procedures in §§ 312.80 through 312.88), especially where no satisfactory alternative therapies exist. In addition, FDA has issued regulations for the accelerated approval of certain new drugs (subpart H of part 314 procedures in §§ 314.500 through 314.560) and biological products (subpart E of part 601 procedures in §§ 601.40 through 601.46) for serious or life-threatening diseases. For instance, accelerated approval can be based on a surrogate endpoint that reasonably suggests clinical benefit or on evidence of the drug's effect on a clinical endpoint other than survival or irreversible morbidity. On March 29, 1996, President Clinton announced a major initiative undertaken by FDA to make promising new therapies available sooner to American cancer patients with intractable or unresponsive malignancies. Under this initiative, FDA proposes, among other things, to shorten approval times for cancer treatments by recognizing that tumor shrinkage is often an early indication of a treatment's effectiveness and by basing approval of investigational drugs for refractory tumors on evidence of tumor shrinkage.

In view of the agency's commitment to provide expanded access to and accelerated approval of new therapies for life-threatening and serious diseases, this proposed rule is intended to ensure that women with reproductive potential who have a life-threatening disease are not excluded from volunteering for and being included in clinical investigational trials for drug products intended to treat their disease. Although a risk or potential risk of reproductive or developmental toxicity might exist, FDA recognizes that the potential benefits that may be accrued by these women from participation in a study for their disease may outweigh such risks and that the availability of certain safeguards can reduce these risks. (See section IV.C. of this document for a discussion regarding minimizing risks.)

### *B. Ethical Principles*

In developing this proposal, FDA has carefully considered the evolution of thought within the agency and the scientific community and among the public regarding the participation of women in clinical trials and the related risks or potential risks. The agency also has considered the basic ethical principles that underlie clinical research. Current FDA and Department of Health and Human Services regulations related to informed consent and IRB's are based, in large part, on the three ethical principles relevant to human subject research discussed in the Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (the Belmont Report) (44 FR 23192, April 18, 1979). These principles include respect for persons, beneficence, and justice.

The principle of respect for persons usually is cited within the context of being certain that individuals are included in clinical research voluntarily after being fully informed. The principle recognizes the ability of autonomous individuals to make their own decisions about participating in clinical research.

The principle of beneficence requires that the risks associated with a clinical research activity be reasonable in the light of expected benefits. Beneficence also requires that the chance for benefits from participation be maximized, and the risk of possible harms be minimized, consistent with sound research design. In weighing risks and benefits, beneficence also recognizes the results of research as a potential benefit, so long as the rights of research participants are protected.

The principle of justice requires that the burdens and benefits of participation in clinical research be equitably distributed across the entire population in the place or region where the clinical research is conducted. In general, racial, ethnic, gender, and economic status should not be used as a basis for excluding participation in clinical research. Furthermore, persons who are eligible for participation in the

clinical research because of their disease or condition should be provided a reasonable opportunity to be included in the research until the research cohort is fully recruited.

An Institute of Medicine committee recently examined the issue of women in health research (Ref. 3). As part of their deliberations, they highlighted the ethical principle of justice and recommended that the scientific community and the institutions that support it ensure that scientific advances in medicine and public health fairly benefit all people, regardless of gender, race, ethnicity, or age. The committee concluded that clinical trials should be conducted consistent with the principle that medical research promotes the health and well-being of both women and men. This proposed rule would help achieve that goal by ensuring that women with a life-threatening disease are not denied the opportunity to contribute to the body of scientific knowledge about their disease and its manifestations in women.

The proposed rule is consistent with the three ethical principles in the Belmont Report and would help to ensure that women with reproductive potential who suffer from a life-threatening disease are no longer excluded from early clinical research.

*C. Informed Consent and Other Mechanisms for Protecting People With a Life-Threatening Disease in Early Clinical Trials*

A number of mechanisms are in place to protect participants in early clinical trials, including requirements for sound study design, the use of sound research procedures, and the proper use of the informed consent process. In addition to the sponsors, who have the responsibility of designing safe clinical trials, and the investigators, who carry them out, institutional review boards (IRB's) play an important role in ensuring participant safety in clinical trials. It is the responsibility of the involved IRB to determine that specific criteria for the protection of study participants are met before approving research subject to the IND regulations (§ 56.111(a) (21 CFR 56.111(a))). For example, the IRB must determine that risks to study participants are minimized by the use of procedures consistent with sound research design and that risks to study participants are reasonable in relation to anticipated benefits (§ 56.111(a)(1) and (a)(2)). The IRB also is responsible for ensuring that information given to study participants as part of the informed consent process is in accordance with FDA's regulations under part 50 (see § 56.111(a)(4)).

Elements of informed consent require that potential study participants be adequately informed that the study involves research (§ 50.25(a)(1)) and of any foreseeable risks or discomforts (§ 50.25(a)(2)). In addition, prospective study participants must be informed, when appropriate, of certain unforeseeable risks, including potential risks to the embryo or fetus, should a female study participant become pregnant (§ 50.25(b)(1)). As FDA noted in the 1993 guideline, if animal reproductive toxicity studies are complete, the results and an explanation of their significance in humans should be presented as part of the informed consent process (58 FR 39406 at 39411). If these studies are not complete, that fact should be communicated along with any other pertinent information, such as a general assessment of reproductive and fetal toxicity associated with other drugs that have related chemical structures or pharmacological effects. If no relevant information is available, the informed consent should explicitly state that fact and make clear that the potential exists for reproductive risks and/or developmental risks to a fetus. If needed, the IRB should require that a specific period of time lapse between when the potential study participants receive relevant information and when they must decide whether to participate in the study. If in the IRB's judgment, additional information to that required by § 50.25 would add meaningfully to the protection of the rights and welfare of study participants, the IRB may require the imparting of that information to the study participants (21 CFR 56.109(b)).

It is also the responsibility of the IRB to determine that the study is designed in such a way as to minimize the risk of fetal exposure to possibly harmful agents. Developmental toxicity has been linked to maternal exposure to certain drugs. Although a link between paternal drug exposure and developmental toxicity has not been conclusively established, results of some studies suggest that paternal exposure to certain drugs might be associated with developmental toxicity (Ref. 4). In particular, low-level, chronic genotoxic exposures that maintain fertility might lead to fetal developmental abnormalities, particularly when there is exposure of post-stem cell stages of spermatozoal development. Although the agency has not issued formal guidance on this issue, in such cases, it might be prudent to take precautions to prevent impregnation of women by men participating in such investigational studies.

The risk of fetal exposure can be eliminated by preventing pregnancy (except in those studies designed to test a drug's effect during pregnancy). The risk of fetal exposure also can be minimized by sponsors and IRB's, who can require the use of pregnancy testing to detect unsuspected pregnancy prior to initiation of study treatment or at intervals during the course of drug exposure. When the study design permits, sponsors can minimize potential developmental risks by short-term timing of studies to coincide with the early follicular phase of the menstrual cycle. Thus, in most of these short-term studies, the investigational agent would be eliminated from a woman's body prior to conception, should she inadvertently become pregnant. When the teratogenic effects of a drug are well established, the agency, sponsor, or IRB may require the use of contraception to prevent pregnancy in sexually active individuals of childbearing potential.

Women and men can eliminate the possibility of pregnancy through abstinence and reduce the possibility of pregnancy through the use of contraception for the duration of drug exposure (which may exceed the length of the study). In part because the cooperation of the individual's sexual partner may be needed to ensure that abstinence occurs, or that appropriate contraceptive methods are used, it is important for potential study participants to be provided with an opportunity to discuss their involvement in a clinical trial with their sexual partner prior to deciding whether to participate in the study.

The agency believes that, through the proper use of the informed consent process and the use of other study design mechanisms, risks to participants in early clinical trials can be reduced. When deciding whether to participate in a clinical trial for an investigational drug, potential participants should be able to weigh, in consultation with their spouse or partner, their health care provider, and their researcher, the potential risks of their participation.

*D. Expanding the Collection of Gender-Specific Data*

As noted previously, the need for gender specific data was the subject of guidances developed by the agency in 1988 and 1993 and was addressed in a proposed rule issued in 1995. Recently, medical and scientific issues related to gender analyses were the subject of an FDA-sponsored workshop on ''Gender Studies in Product Development:

Scientific Issues and Approaches'' held from November 6 to 7, 1995 (Ref. 5). Workshop participants, including representatives from industry, academia, government agencies, consumer groups, and patient communities, concluded that women should be included in all stages of drug development to fully characterize the safety and efficacy profile of the product. It was noted by numerous participants that use of gender-specific data from early trials may improve the efficiency of phase 3 trials by aiding in the interpretation of expected variations among gender groups.

In the 1993 guideline, FDA acknowledged that although drugs often behave similarly in demographic (age, gender, race) and other (concomitant disease, concomitant drugs) subsets of the population, there are many differences within such subsets, for example, in dose-response, in maximum size of effect, or in the risk of an adverse effect (58 FR 39406 at 39409). To identify such potential differences and to help refine labeling information, patient selection, and dose selection, the agency believes that it is important that those women who are likely to use an investigational agent once it is marketed be included in clinical investigations that may identify potential gender differences. In the case of HIV and AIDS, many of the women who are affected are young women with reproductive potential. Therefore, early participation by these women in clinical trials for such diseases will help ensure that needed gender-specific safety and effectiveness data are available for the women affected by the disease (Ref. 6).

## V. Legal Authority

Section 505(i) (21 U.S.C. 355(i)) of the Federal Food, Drug, and Cosmetic Act (the act) confers broad authority upon the Secretary of Health and Human Services (the Secretary) (and by delegation to FDA) to issue regulations governing the clinical investigation of new drugs to protect the rights, safety, and welfare of human subjects (including through informed consent provisions) and otherwise to protect the public health. In addition, section 701 of the act (21 U.S.C. 371) provides that the Secretary has authority to issue regulations for the efficient enforcement of the act (including the drug-related provisions, such as the misbranding and approval provisions of sections 502 (21 U.S.C. 352) and 505 of the act.

The proposed amendment to the clinical hold regulations is intended to protect human subjects against being categorically excluded, based on reproductive potential, from the opportunity to participate in clinical trials investigating potentially beneficial treatments for a life-threatening disease. In addition, the proposed amendment would enhance public health protection by expanding opportunities to generate data concerning the safety and efficacy of investigational drugs for the treatment of life-threatening diseases.

The agency believes that prohibiting the exclusion of women with reproductive potential who have a life-threatening disease from clinical trials also is consistent with congressional efforts to prevent unwarranted discrimination against women. In the employment context, for example, the Civil Rights Act of 1964, as amended by the Pregnancy Discrimination Act (42 U.S.C. 2000e(k), 2000e–2(e)(1)) and as interpreted by the U.S. Supreme Court in the landmark case of *International Union, United Automobile, Aerospace and Agricultural Implement Workers, UAW* v. *Johnson Controls, Inc.*, 111 S.Ct. 1196 (1991), prohibits the exclusion of women with childbearing capacity from jobs they are qualified to perform solely because the working conditions of those jobs pose potential risks to exposed fetuses. Although the Court did not consider or hold that the Civil Rights Act applies to clinical drug trials, which are manifestly different in nature and purpose from private employment, FDA believes it is appropriate to consider the Court's opinion when developing policy on the eligibility of women with reproductive potential for participation in clinical trials for a life-threatening disease.

## VI. Description of the Proposed Rule

Current § 312.42(b)(1) identifies the grounds for placing a clinical hold on proposed or ongoing phase 1 studies under an IND, and current § 312.42(b)(2) identifies the grounds for placing a clinical hold on proposed or ongoing phase 2 or phase 3 studies. FDA is proposing to amend §§ 312.42(b)(1) and (b)(2) to provide an additional ground for placing a phase 1, phase 2, or phase 3 study under an IND on clinical hold. Under proposed §§ 312.42(b)(1)(v) and (b)(2)(i), FDA may issue a clinical hold on any proposed or ongoing clinical trial for a life-threatening illness or disease that affects both genders if men or women with reproductive potential who have the disease being studied are excluded from eligibility in any phase of clinical investigation because of a risk or potential risk of reproductive toxicity (i.e., toxicity to reproductive organs) or developmental toxicity (i.e., toxicity to potential offspring) from use of the investigational drug. FDA believes that such risks would be outweighed by the potential benefits that may be accrued by participants in a study for the treatment of their disease and that fully informed potential participants should be able to make their own risk-benefit determination. FDA also believes that, in the case of developmental toxicity, potential risks can be minimized by the prevention of pregnancy through contraception or abstinence.

The clinical hold under proposed §§ 312.42(b)(1)(v) and (b)(2)(i) would not apply to clinical studies conducted: (1) Exclusively in healthy volunteers; (2) under special circumstances, such as studies of a single-gender population (e.g., studies evaluating the excretion of a drug in semen or its effects on menstrual function); or (3) in men, as long as a study that does not exclude subjects with reproductive potential has been planned or is being conducted in women.

The phrase ''women with reproductive potential'' as used in the proposed rule does not include pregnant women. The proposed rule also would not impose requirements to enroll or recruit a specific number of men or women with reproductive potential.

As is true for clinical holds on any basis, FDA ordinarily would issue a clinical hold only after attempts to convince the sponsor to remove an exclusion had failed (§ 312.42(c)).

Under proposed § 312.42(b)(1)(v), ''life-threatening illnesses or diseases'' are defined as ''diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted.'' The proposed definition is consistent with the definition of ''life-threatening'' in the IND regulations governing drugs intended to treat life-threatening illnesses (21 CFR 312.81(a)(1)).

The proposed definition of life-threatening illnesses or diseases is intended to include those fatal diseases where death itself may not be imminent, but where treatment is necessary to prevent premature death. For example, an anti-retroviral drug might be found, on the basis of phase 2 studies, to delay progression from the asymptomatic state to the symptomatic state and then to AIDS when used early after infection with HIV. Although this progression ordinarily would take more than 12 months to occur in most patients, this condition would be within the definition of life-threatening. Other examples of life-threatening illnesses include cancer, certain cardiac arrhythmias, intracranial hemorrhage, or amyotrophic lateral sclerosis.

The exclusion of subjects with reproductive potential addressed by this proposed rule not only includes explicit

exclusion but also de facto exclusion. For example, a de facto exclusion might result from setting study entry criteria that require sterilization and would have the effect of precluding enrollment of participants with reproductive potential. De facto exclusions also might result from setting criteria that are inherently difficult for subjects to meet, such as weight, or other physical requirements that generally differ between women and men.

**VII. 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.

**VIII. Paperwork Reduction Act of 1995**

This proposed rule does not contain any information collection provisions that would be subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520).

**IX. Analysis of 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). 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 Regulatory Flexibility Act requires agencies to analyze regulatory options if the proposed rule is expected to have a significant impact on a substantial number of small entities.

The Unfunded Mandates Reform Act (Pub. L. 104–4) requires that agencies prepare an assessment of anticipated costs and benefits before proposing any rule that may result in an annual 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). This proposed rule does not impose any mandates on State, local, or tribal governments, or the private sector that will result in an annual expenditure of $100,000,000 or more. The data for the impacts analysis were developed by FDA's Economics Staff, Office of Management and Systems, Office of Planning and Evaluation, and their full report is on file at the Dockets Management Branch (address above).

*A. Costs*

Implementation of this proposed rule could impart additional direct costs to the industry in one area—the cost associated with testing for pregnancy in women with reproductive potential who volunteer to participate in clinical trials that would have previously excluded them.

As fully described in its detailed study (Ref. 7), FDA estimated the direct cost in the following manner. Using an FDA protocol database, the agency estimated the number of clinical trials for drug products for life-threatening diseases from which women with reproductive potential are being excluded. The agency then determined the total number of subjects recruited for those clinical trials. Using published information, the agency estimated the relative incidence among women with reproductive potential for the specific life-threatening diseases compared to the incidence in the general population. Using the estimates of relative incidence among women with reproductive potential for the specific disease, it was estimated how many women would be participating in clinical trials for the specific disease, were they not being excluded. Finally, using the approximate length of each phase of clinical trials (phases 1, 2, and 3), the agency calculated the number of pregnancy tests that would be necessary to test for pregnancy in this volunteering population subset.

FDA conducted its analysis using data extracted from the majority of the clinical trial protocols submitted to four review divisions in the Center for Drug Evaluation and Research (CDER) during a 20-month period between August 1, 1993, and March 31, 1995: Cardio-Renal; Anti-Viral; Medical Imaging, Surgical and Dental; and the former Pilot Drug Evaluation. The protocol data base includes information on the phase of the studies (whether they are phase 1, 2, or 3), the planned size of the trials, and the indications for which the therapies are being studied. Data from this data base were analyzed to estimate how many protocols were submitted to these four FDA divisions involving life-threatening illnesses that excluded women with reproductive potential. Forty-three protocols involving life-threatening illnesses and excluding women with reproductive potential were identified as having been submitted to FDA during this 20-month period.

Projecting the number of submissions from the four review divisions across the entire agency required additional analysis because it could not be assumed that all review divisions receive protocols for life-threatening diseases at the same rate. To adjust for the difference from division to division, the agency calculated the number of NDA approvals that were granted in each division for drugs to treat life-threatening and severely debilitating illnesses under the accelerated approval procedures of subpart E of part 312. Using the results of this analysis and the annualized numbers from the four analyzed review divisions, it was possible to calculate approximately how many protocols for life-threatening diseases that exclude women are submitted to individual review divisions each year. It was projected that approximately 62 protocols are submitted to FDA per year for life-threatening diseases that exclude women with reproductive potential.

Next it was assumed that, once they are no longer excluded, women with reproductive potential would enter clinical trials in proportion to the relative incidence of the disease occurrence in that population at diagnosis. Using published data on the relative incidence among women with reproductive potential at diagnosis of AIDS, HIV, and coronary heart disease and the number of protocols submitted to the four divisions projected across the entire agency and annualized, the agency estimated how many women (ages 13 to 49 years) are excluded per year from phase 1, phase 2, and phase 3 clinical studies in the United States. The results showed that approximately 90 women with reproductive potential are excluded from phase 1 studies, 266 from phase 2 studies, and 40 from phase 3 studies annually in the United States.

If one assumes further that phase 1 studies last approximately 2 weeks, phase 2 studies approximately 3 months, and phase 3 studies about a year, the costs for pregnancy testing can be assessed. During phase 1 studies, approximately 1 pregnancy test would be required for each woman with reproductive potential entering the study; during phase 2 studies, approximately 3 tests would be required; and, during phase 3 studies, approximately 12 tests would be required. At a cost of $30 per test, the annual cost to industry is estimated to be at most about $41,000. This estimate is summarized in Table 1.

TABLE 1.—ESTIMATED ANNUAL COSTS OF TESTING FOR PREGNANCY IN WOMEN WITH REPRODUCTIVE POTENTIAL IN U.S. CLINICAL TRIALS FOR THERAPIES FOR LIFE-THREATENING ILLNESSES

| Study Phase | Tests Required per Woman | Estimated Number of Women Annually | Cost per Test | Annual Costs |
|---|---|---|---|---|
| 1 | 1 | 90 | $30 | $2,700 |
| 2 | 3 | 266 | $30 | $23,940 |
| 3 | 12 | 40 | $30 | $14,400 |
| Totals | | 396 | | $41,040 |

The largest cost encountered in the 43 analyzed protocols was a phase 2 trial from which an estimated 45 women with reproductive potential were excluded. The cost of pregnancy testing for this trial, if women with reproductive potential had been included, would have been about $4,050. Of the 43 protocols analyzed, 6 had estimated costs of pregnancy testing exceeding $1,000.

The agency is aware of industry's concerns about the liability exposure associated with the inclusion of women with reproductive potential in clinical trials, particularly prior to completion of animal reproductive studies. FDA believes, however, that the inclusion in investigational studies of women with reproductive potential who have a life-threatening disease and who have given informed consent is not likely to lead to increased liability. Informed consent means that a study participant has agreed to participate despite recognition and appreciation of known or potential risks, an agreement that should minimize the legal risks associated with drug development. Careful use of study design and informed consent is likely to minimize exposure to liability (Refs. 8 and 9). There is, of course, no way to guarantee this, but there have been few instances of liability assessed against drug manufacturers for the conduct of clinical trials.

As already stated, if a deficiency exists in a clinical investigation that may be grounds for the imposition of a clinical hold, FDA will generally attempt to discuss and satisfactorily resolve the matter with the sponsor before issuing the clinical hold order (§ 312.42(c)). An IND would be placed on clinical hold for specifically excluding women with reproductive potential only as a last resort. Only for those few protocols could there be an increase in cost, due primarily to a delay in starting the clinical trials.

The agency believes that the societal benefits more than outweigh the potential minimal additional costs because a considerable patient population (women with reproductive potential who have a life-threatening disease) could receive a potentially beneficial new therapy.

*B. Small Entities*

The protocol analysis identified protocols sponsored by small businesses. The largest additional pregnancy testing cost incurred by a small business in the reviewed protocols under the proposed rule was $990. Projected across all CDER/CBER review divisions and annualized, we expect no more than nine protocol submissions per year from small businesses that might incur additional costs under the proposed rule. Few small firms are likely to be affected in any given year and most of these would incur no significant additional costs. Therefore, under the Regulatory Flexibility Act, the Commissioner of Food and Drugs certifies that this rule will not have a significant effect on a substantial number of small entities.

## X. Request for Comments

Interested persons may, on or before December 23, 1997, submit to the Dockets Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one 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 office above between 9 a.m. and 4 p.m., Monday through Friday.

## XI. References

Copies of the following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. McGovern, T., ''Proposal to Eliminate Obstacles Facing Women in the Drug Development Process: A Recommendation to the National Task Force on AIDS Drug Development,'' HIV Law Project of the AIDS Service Center, June 30, 1994.

2. Transcript of the meeting of the National Task Force on AIDS Drug Development, October 28, 1994 (see discussion on pp. 25 to 70).

3. Mastroianni, A. C., R. Faden, and D. Federman, editors, *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Vol. 1, National Academy Press, Washington, pp. 75–83, 1994.

4. DeLap, R. J., J. L. Fourcroy, and G. A. Fleming, ''Fetal Harm Due to Paternal Drug Exposure: A Potential Issue in Drug Development,'' *Drug Information Journal*, 30:359–364, 1996.

5. Transcript of the FDA workshop ''Gender Studies in Product Development: Scientific Issues and Approaches,'' November 6–7, 1995.

6. Sherman, L. A., R. Temple, and R. B. Merkatz, ''Women in Clinical Trials: An FDA Perspective,'' *Science*, 269:793–795, 1995.

7. Food and Drug Administration, Office of Management and Systems, Office of Planning and Evaluation, *Impacts of Not Excluding Women with Reproductive Potential Who Have Life-threatening Illnesses from Clinical Trials*, January 10, 1997.

8. Flannery, E., and S. N. Greenberg, ''Liability Exposure for Exclusion and Inclusion of Women as Subjects in Clinical Studies,'' in *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Vol. 2, edited by A. C. Mastroianni, R. Faden, and D. Federman, National Academy Press, Washington, pp. 96–97, 1994.

9. Clayton, E. W., ''Liability Exposure When Offspring Are Injured Because of Their Parents' Participation in Clinical Trials,'' in *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Vol. 2, edited by A. C. Mastroianni, R. Faden, and D. Federman, National Academy Press, Washington, pp. 108–109, 1994.

## List of Subjects in 21 CFR Part 312

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

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service 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 continues to read as follows:

**Authority:** Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701 of the Federal Food, Drug,

and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371); sec. 351 of the Public Health Service Act (42 U.S.C. 262).

2. Section 312.42 is amended by adding new paragraph (b)(1)(v) and by revising paragraph (b)(2)(i) to read as follows:

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

* * * * *

(b) * * *

(1) * * *

(v) The IND is for the study of an investigational drug intended to treat a life-threatening illness or disease that affects both genders, and men or women with reproductive potential who have the disease being studied are excluded from eligibility in any phase of clinical investigation because of a risk or potential risk of reproductive (i.e., toxicities to reproductive organs) or developmental (i.e., toxicities to potential offspring) toxicity from use of the investigational drug. The phrase ''women with reproductive potential'' does not include pregnant women. For purposes of this paragraph, ''life-threatening illnesses or diseases'' are defined as ''diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted.'' The clinical hold would not apply under this paragraph to clinical studies conducted:

(A) Under special circumstances, such as studies of a single-gender population (e.g., studies evaluating the excretion of a drug in semen or the effects on menstrual function); or

(B) In men, as long as a study that does not exclude subjects with reproductive potential has been planned or is being conducted in women.

(2) * * *

(i) Any of the conditions in paragraphs (b)(1)(i) through (b)(1)(v) of this section apply; or

* * * * *

Dated: September 16, 1997.

**Michael A. Friedman,**

*Lead Deputy Commissioner for the Food and Drug Administration.*

**Donna E. Shalala,**

*Secretary of Health and Human Services.*

[FR Doc. 97–25268 Filed 9-23-97; 8:45 am]

BILLING CODE 4160–01–F

## DEPARTMENT OF THE INTERIOR

## Fish and Wildlife Service

## 50 CFR Part 17

**RIN 1018–AE30**

## Endangered and Threatened Wildlife and Plants; Public Hearing and Extension of Comment Period on Proposed Endangered Status for Keck's Checker-Mallow

**AGENCY:** Fish and Wildlife Service, Interior.

**ACTION:** Proposed rule; notice of public hearing and extension of comment period.

**SUMMARY:** The Fish and Wildlife Service (Service), pursuant to the Endangered Species Act of 1973, as amended (Act), provides notice of a public hearing and extension of the comment period on the proposed endangered status for *Sidalcea keckii* (Keck's checker-mallow). The comment period is extended to accommodate a public hearing that was requested by California Assemblyman Roy Ashburn, Thirty-Second District.

**DATES:** The public hearing will be held on Tuesday, October 21, from 6:00 p.m. to 8:00 p.m. in Visalia, California. The comment period closes November 10, 1997.

**ADDRESSES:** The public hearing will be held at the Visalia Convention Center, 303 East Acequia Street, Visalia, California. Comments and materials concerning this proposal should be sent to the Field Supervisor, U.S. Fish and Wildlife Service, Sacramento Fish and Wildlife Office, 3310 El Camino Avenue, Suite 130, Sacramento, California 95821–6340. Comments and materials received will be available for public inspection, by appointment, during normal business hours at the above address.

**FOR FURTHER INFORMATION CONTACT:** Ken Fuller of the Sacramento Fish and Wildlife Office (see **ADDRESSES** section) at (916) 979–2120.

**SUPPLEMENTARY INFORMATION:**

### Background

On July 28, 1997, the Service published a rule proposing endangered status for *Sidalcea keckii* in the **Federal Register** (62 FR 40325). The original comment period was to close on September 26, 1997. Section 4(b)(5)(E) of the Act (16 U.S.C. 1531 *et seq.*) requires that a public hearing be held if it is requested within 45 days of the publication of the proposed rule. In response to a request for a public hearing from California Assemblyman Roy Ashburn, a public hearing will be held in Visalia, California on October 21, 1997, at the Visalia Convention Center. Parties wishing to make statements for the record should bring a copy of their statements to the hearing. Oral statements may be limited in length, if the number of parties present at the hearing necessitates such a limitation. There are no limits to the length of written comments or materials presented at the hearing or mailed to the Service. Written comments carry the same weight as oral comments. The comments period now closes on November 10, 1997. Written comments should be submitted to the Service in the **ADDRESSES** section.

*Sidalcea keckii* is an annual plant that is known from one population in the hilly annual grasslands of south-central Tulare County. The plant is threatened by agricultural land conversion, urban development, and naturally occurring events. Comments from the public regarding the accuracy of this proposed rule are sought, especially regarding:

(1) Biological, commercial trade, or other relevant data concerning any threat (or lack thereof) to the species listed above;

(2) The location of any additional populations of the species and the reasons why any habitat should or should not be determined to be critical habitat as provided by section 4 of the Act;

(3) Additional information concerning the range, distribution, and population sizes of the species; and

(4) Current or planned activities in the subject area and their possible impacts on the species.

### Author

The primary author of this notice is Ken Fuller (see **ADDRESSES** section).

### Authority

The authority for this action is the Endangered Species Act of 1973 (16 U.S.C. 1531 *et seq.*).

Dated: September 16, 1997.

**Cynthia Barry,**

*Acting Regional Director, Region 1, Portland, Oregon.*

[FR Doc. 97–25061 Filed 9–23–97; 8:45 am]

BILLING CODE 4310–55–P