

43025, August 22, 1994), and by adding a new airworthiness directive (AD), to read as follows:

Jetstream Aircraft, Limited: Docket 94-NM-237-AD. Supersedes AD 94-17-12, Amendment 39-9007.

Applicability: Model 4101 airplanes; having constructors numbers 41004 through 41015 inclusive, 41018 through 41026 inclusive, 41028 through 41030 inclusive, and 41032; certificated in any category.

Note 1: This AD applies to each airplane 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 airplanes that have been modified, altered, or repaired so that the performance of the requirements of this AD is affected, the owner/operator must use the authority provided in paragraph (d) of this AD to request approval from the FAA. This approval may address either no action, if the current configuration eliminates the unsafe condition; or different actions necessary to address the unsafe condition described in this AD. Such a request should include an assessment of the effect of the changed configuration on the unsafe condition addressed by this AD. In no case does the presence of any modification, alteration, or repair remove any airplane from the applicability of this AD.

Compliance: Required as indicated, unless accomplished previously.

To prevent uncommanded extension of the lift spoiler in the event of loss of hydraulic pressure in the spoiler actuator, accomplish the following:

(a) Within 21 days after September 6, 1994 (the effective date of AD 94-17-12, amendment 39-9007), remove the spoiler actuators in accordance with Jetstream Alert Service Bulletin J41-A27-034, dated June 9, 1994, or Revision 1, dated October 28, 1994. Following removal of the actuators, accomplish the requirements of paragraphs (a)(1) and (a)(2) of this AD, in accordance with the service bulletin. Thereafter, repeat the requirements of this paragraph at intervals not to exceed 500 landings.

(1) Prior to further flight, purge the hydraulic system to ensure that there is no contamination.

(2) Prior to further flight, install a spoiler actuator that has been previously certified and marked with an "R" after the serial number on the nameplate of the actuator.

(b) For spoiler actuators having Lucas Aerospace part number (P/N) TY1763-01A or P/N TY1763-01B: Prior to the accumulation of 5,000 total hours time-in-service on the spoiler actuator, or within 30 days after the effective date of this AD, whichever occurs later, replace the actuator with a new or serviceable part, in accordance with Jetstream Service Bulletin J41-A27-034, Revision 1, dated October 28, 1994. Thereafter, prior to the accumulation of 5,000 hours time-in-service on the spoiler actuator, replace the actuator with a new or serviceable part, in accordance with the service bulletin. Such replacement constitutes terminating action for the

repetitive purging and repetitive installation requirements of paragraph (a) of this AD.

(c) Installation of improved spoiler actuators (Modification JM 41381) on the left and right wings, in accordance with Jetstream Service Bulletin J41-27-037, dated November 7, 1994, constitutes terminating action for the requirements of paragraphs (a) and (b) of this AD.

(d) 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, Standardization Branch, ANM-113, FAA, Transport Airplane Directorate. Operators shall submit their requests through an appropriate FAA Principal Maintenance Inspector, who may add comments and then send it to the Manager, Standardization Branch, ANM-113.

Note 2: Information concerning the existence of approved alternative methods of compliance with this AD, if any, may be obtained from the Standardization Branch, ANM-113.

(e) 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 airplane to a location where the requirements of this AD can be accomplished.

Issued in Renton, Washington, on September 1, 1995.

Darrell M. Pederson,

Acting Manager, Transport Airplane Directorate, Aircraft Certification Service.
[FR Doc. 95-22302 Filed 9-7-95; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 312 and 314

[Docket No. 95N-0010]

Investigational New Drug Applications and New Drug Applications

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend its regulations pertaining to investigational new drug applications (IND's) and new drug applications (NDA's). The proposed rule would clearly define in the NDA format and content requirements the need to present effectiveness and safety data for important demographic subgroups, specifically gender, age, and racial subgroups. The rule would codify expectations that FDA has previously described in guidance. The proposed amendments would also require IND sponsors of drugs, including biological

products, to characterize, in their annual reports, the number of subjects in a clinical study according to age group, gender, and race. The proposed rule does not address the requirements for the conduct of clinical studies and would not require sponsors to conduct any more studies than they have already conducted. It also would not require the inclusion of particular numbers of individuals from specific subgroups in any study or overall. The rule refers only to the presentation of data already collected. The scope of this proposal does not extend to requiring additional studies or data.

DATES: Written comments by December 7, 1995.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Deborah A. Wolf, Center for Drug Evaluation and Research (HFD-362), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-594-1046.

SUPPLEMENTARY INFORMATION: The proposed rule would amend the NDA content and format regulations at 21 CFR 314.50 to explicitly require that sponsors submit effectiveness and safety data by gender, age, and racial subgroups and other subgroups of the population of patients treated, as appropriate, such as patients with renal failure or patients with different levels of severity of disease. In the **Federal Register** of July 22, 1993 (58 FR 39406), FDA published a guideline entitled "Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs." The guideline provided guidance on FDA's expectations regarding inclusion of both men and women 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 preamble to the guideline described the development of the agency's policy regarding the evaluation of clinical data by gender. The guideline noted that over the preceding decade there had been growing concern that the drug development process did not produce adequate information about the effects of drugs in women (58 FR 39406). Analyses of published clinical trials in certain therapeutic areas had indicated that there had been little or no participation by women in many of the studies. There had also been little study of the effects of such aspects of female

physiology as the menstrual cycle and menopause or of the effects of oral contraceptives and systemic progestins and estrogens on drug action and pharmacokinetics.

The guideline also explained that concerns about the adequacy of data on the effects of drugs in women have arisen in the context of an increasing awareness of the need to individualize treatment in the face of the wide variety of demographic, disease-related, and individual patient-related factors that can lead to different responses in subsets of the population. Optimal use of drugs requires identification of these factors so that appropriate adjustments in dose, concomitant therapy, or monitoring can be made. The guideline was part of FDA's effort to address the need to gather and evaluate data from various subpopulations in clinical drug trials. The agency had previously addressed the need to develop information on the elderly in the 1989 guideline entitled, "Guideline for the Study of Drugs Likely to be Used in the Elderly." That guideline provided similar guidance regarding inclusion of elderly patients in clinical trials and assessment of clinical and pharmacokinetic differences between older and younger patients.

In 1983 and 1989, FDA examined the relative numbers of individuals from two important demographic subgroups, women and the elderly, in the data bases of NDA's. The agency found that, in general, the proportions of women and men included in the clinical trials were similar to the respective proportions of women and men who had the diseases for which the drugs were being studied, taking into account the age range of the population studied. The General Accounting Office (GAO) conducted a larger study of drugs approved during the period 1988 through 1991, and found similar proportions. Women were found to typically represent a majority of patients in NDA data bases of drugs used to treat conditions more common, or more commonly treated, in women, and a minority, generally a sizable one, in tests of drugs for conditions that occur predominantly in males in the age range usually included in the clinical trials.

Although women have been included in the later phases of clinical trials, the agency believes that inclusion alone is not sufficient for adequate assessment of potential gender differences. There must be an effort to use the data to discover such differences, and the agency found that this effort was not made. Various documents published by the agency have reflected the need to examine gender as well as other characteristics

for their effects on drug response. FDA's regulations on NDA content and format require the clinical data section of the NDA to include, among other things, "An integrated summary of the data demonstrating substantial evidence of effectiveness for the claimed indications. Evidence is also required to support the dosage and administration section of the labeling, including support for the dosage and dose interval recommended, and modifications for specific subgroups (for example, pediatrics, geriatrics, patients with renal failure)" and an integrated summary of safety. (See 21 CFR 314.50(d)(5)(v) and (d)(5)(vi)(a)). The examples of subgroups listed in § 314.50(d)(5)(v) were not intended to be a complete list or to limit the subgroups for which data should be submitted. In 1988, in a guideline entitled, "Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications," FDA discussed analyses of population subsets within NDA data bases to look for differences in effectiveness and adverse reactions to drugs. The guideline describes the population subsets to include subsets such as different genders, age groups, and races, and other subsets such as people receiving other drug therapy and people with concurrent illnesses. See, "Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications" at pages 32 and 40. The guideline describes the need for clinical data beyond the specific subgroups and categories of information set forth in the current regulations.

The current wording of § 314.50, while not intended to limit the analyses to be carried out does not fully reflect the need to present the safety and effectiveness data by subgroup and omits important subgroups, including gender and racial groups. The proposal would make explicit the agency's requirements concerning the data that are presented in NDA's. It would make clear the need to present safety and effectiveness data by gender, age, and racial subgroups to allow a determination, to the extent the data permit, of whether these factors affect results of treatment or alter dosing requirements.

FDA believes that it is important to make such an explicit requirement. After the publication of the 1988 guideline, FDA and GAO examined data bases for NDA's to see whether the analyses to which the guideline refers were being conducted and submitted. Both of the examinations found that in about half of the cases the data bases were not being analyzed to determine

whether there were differences in response to drugs between the two genders or among different racial groups and age groups. Thus, changes that the proposal would make to § 314.50 would codify what the agency has already identified as important elements of clinical data.

FDA also believes that to codify the need for presentations of data by subgroups will provide industry with clear information regarding potential consequences of the absence of subgroup data. The agency's regulation governing the filing of an application, which is set forth in 21 CFR 314.101, provides that the Center for Drug Evaluation and Research may refuse to file an NDA that, among other things, is not submitted in the form required under § 314.50 or that is incomplete because it does not on its face contain information required under section 505(b) of the Federal Food, Drug and Cosmetic Act. 21 CFR 314.101(d)(3). The refusal to file policy attempts to direct FDA's resources to applications complete enough for review. The agency's "New Drug Evaluation Guidance Document: Refusal to File" describes situations in which FDA applies the provision in § 314.101(d)(3) to make refusal to file decisions. In particular, the document explains that omission of critical data, information or analyses needed to evaluate effectiveness and safety or provide adequate directions for use is an appropriate basis for a refusal to file. Among the particular considerations in refusal to file decisions is a "clearly inadequate evaluation for safety and/or effectiveness of the population intended to use the drug, including pertinent subsets, such as gender, age, and racial subsets." Thus, the proposal would allow sponsors to know from the beginning that data that are not presented with regard to gender, age, and racial groups are grounds for a refusal to file.

It is important to note that the rule does not address the requirements for the conduct of clinical studies and that this proposal would not require sponsors to conduct any more studies than they have already conducted. It also does not require the inclusion of particular numbers of individuals from specific subgroups in any study or overall. The rule refers only to the presentation of data already collected. The scope of this proposal does not extend to requiring additional studies or data.

Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) 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.

Paperwork Reduction Act of 1980

This proposed rule contains information collections which are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1980. The title, description, and respondent

description of the information collection are shown below with an estimate of the annual reporting and recordkeeping burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.

Title: Investigational New Drug Applications and New Drug Applications.

Description: The information submitted by respondents pursuant to

the proposed regulatory revisions would assist the agency in monitoring the success of drug companies in enrolling in clinical drug trials subjects representing various subgroups of the population expected to use the drug being tested once it is approved and marketed and in better evaluating the safety and efficacy profiles of drugs for various subgroups.

Description of respondents: Businesses, nonprofit institutions, small businesses.

Section	Annual number of respondents	Annual frequency	Average burden per response	Annual burden hours
312.33(a)(2)	1,616 (noncommercial).....	1	2 hours	3,232
312.33(a)(2)	362 (commercial) ..	1	8 hours	2,896
314.50	50	1	40 hours	2,000
Total	8,128

The agency has submitted a copy of this proposed rule to OMB for review of these information collections. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to FDA's Dockets Management Branch (address above) and to the Office of Information and Regulatory Affairs, OMB, Washington, DC 20503.

Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (Pub. L. 96-354). 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 consistent with the regulatory philosophy and principles identified in the Executive Order. The proposed rule does not require any change in the studies a drug manufacturer needs to conduct or impose any requirements on the conduct of those studies. It requires only a presentation of data already collected. In addition, the proposed rule is not a significant regulatory action as defined by the Executive Order and so is not subject to review under the Executive Order.

This proposed rule would amend the IND regulations to enable FDA and

sponsors of drugs, including biological products, to monitor the sponsor's success in studying the populations that are likely to receive the drug once it is approved. Under the current IND regulations in § 312.33(a)(2) (21 CFR 312.33(a)(2)), sponsors are required to submit an annual report that includes for each study, among other things, "The total number of subjects initially planned for inclusion in the study, the number entered into the study to date, the number whose participation in the study was completed as planned, and the number who dropped out of the study for any reason." The proposed rule would amend § 312.33(a)(2) to require that the annual report include the number of subjects entered into the study "characterized by age group, gender, and race." Reporting and reviewing this information would not itself represent a need for new studies or patients. The agency is aware that many clinical trials do not contain enough patients from various subgroups to perform statistically rigorous comparisons of outcomes between subgroups. The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. The agency certifies that the proposed rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

Request for Comments

Interested persons may, on or before December 7, 1995, 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.

List of Subjects

21 CFR Part 312

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

21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

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 parts 312 and 314 be amended to read 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 312.33 is amended by revising paragraph (a)(2) to read as follows:

§ 312.33 Annual reports.

* * * * *

(a) * * *

(2) The total number of subjects initially planned for inclusion in the study; the number entered into the study to date, characterized by age group, gender, and race; the number whose participation in the study was completed as planned; and the number who dropped out of the study for any reason.

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PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG OR AN ANTIBIOTIC DRUG

3. The authority citation for 21 CFR part 314 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701, 704, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371, 374, 379e).

4. Section 314.50 is amended by revising the second sentence and adding two new sentences after the second sentence in paragraph (d)(5)(v) and by adding two new sentences after the first sentence in paragraph (d)(5)(vi)(a) to read as follows:

§ 314.50 Content and format of an application.

* * * * *

(d) * * *

(5) * * *

(v) * * * Evidence is also required to support the dosage and administration section of the labeling, including support for the dosage and dose interval recommended. The effectiveness data shall be presented by gender, age, and racial subgroups. Effectiveness data from other subgroups of the population of patients treated, as appropriate, such as patients with renal failure or patients with different levels of severity of disease, shall also be presented.

(vi) * * *

(a) * * * The safety data shall be presented by gender, age, and racial subgroups. Safety data from other subgroups of the population of patients treated, as appropriate, such as patients with renal failure or patients with different levels of severity of disease, shall also be presented. * * *

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Dated: July 11, 1995.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 95-22297 Filed 9-7-95; 8:45 am]

BILLING CODE 4160-01-F

DEPARTMENT OF LABOR

Wage and Hour Division

29 CFR Part 552

RIN 1215-AA82

Application of the Fair Labor Standards Act to Domestic Service

AGENCY: Wage and Hour Division, Employment Standards Administration, Labor.

ACTION: Proposed rule; reopening and extension of comment period.

SUMMARY: This document reopens and extends the period for filing written comments on a proposed revision to § 552.109 of Regulations, 29 CFR part 552, which was published in the **Federal Register** on December 30, 1993 (58 FR 69310), to clarify the minimum wage and overtime exemption under the Fair Labor Standards Act (FLSA) for certain employees of third-party employers who provide domestic companionship services. The Department is continuing to consider this particular proposal, and this action is taken in order to obtain additional comments from interested parties. A separate final rule published elsewhere in this issue amends 29 CFR part 552 to incorporate changes necessitated by amendments to Title II of the Social Security Act, which were enacted October 22, 1994, as Pub. L. 103-387 (Social Security Domestic Employment Reform Act), and makes other updating and technical revisions as proposed in the notice of December 30, 1993.

DATES: Comments are due on or before November 7, 1995.

FOR FURTHER INFORMATION CONTACT: Richard M. Brennan, Acting Director, Division of Policy and Analysis, Wage and Hour Division, Employment Standards Administration, U.S. Department of Labor, Room S-3506, 200 Constitution Avenue NW., Washington, DC 20210, (202) 219-8412. This is not a toll-free number.

SUPPLEMENTARY INFORMATION: The Fair Labor Standards Act of 1938 (52 Stat. 1060, as amended; 29 U.S.C. 201 *et seq.*), as amended by the Fair Labor Standards Amendments of 1974 (Pub. L. 93-259, 88 Stat. 55), extended with certain exceptions the FLSA's minimum wage, overtime pay, and recordkeeping

provisions to domestic service employees whose compensation for services would constitute wages under section 209(g) of Title II of the Social Security Act, or who are employed by one or more employers for more than 8 hours in the aggregate in any workweek. Section 13(a)(15) of the FLSA provides an exemption from the minimum wage and overtime pay requirements of the Act for "employees employed on a casual basis in domestic service employment to provide babysitting services," and for domestic service employees employed "to provide companionship services for individuals who * * * are unable to care for themselves." Section 13(b)(21) provides an overtime exemption for domestic service employees who reside in the household in which they are employed. On February 20, 1975, regulations and interpretations implementing the domestic service employment provisions of the FLSA were published in the **Federal Register** (40 FR 7405) at 29 CFR part 552.

The Department published a notice of proposed rulemaking in the **Federal Register** on December 30, 1993 (58 FR 69310), inviting public comments until February 28, 1994, which, among other things, would revise § 552.109 to clarify that, in order for the exemptions in FLSA sections 13(a)(15) and 13(b)(21) to apply, employees engaged in providing companionship services and live-in domestic service employees who are employed by a third-party employer or agency must also be "jointly" employed by the family or household using their services. In addition, the Department invited public comments on certain updating and technical changes to 29 CFR part 552.

The Department proposed to revise § 552.109 to provide, consistent with rulings of the Wage-Hour Administrator, that companions and live-in domestics employed by third-party employers are eligible for the exemptions in FLSA sections 13(a)(15) and 13(b)(21) only where the individuals are also employed by the family or household using their services. This clarification was considered necessary in order to make the underlying definition of "domestic service employees" (*i.e.*, someone who performs services of a household nature "in or about a private home * * * of the person *by whom he or she is employed* * * *") at § 552.101 internally consistent with § 552.109, applicable to domestic service employees who provide "companionship services."

A total of 7 comments were received in response to the notice. All focused their remarks on the proposed revision