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Dated: January 30, 1998.

Janice F. Oliver,

Deputy Director for Systems and Support, Center for Food Safety and Applied Nutrition.

[FR Doc. 98–3357 Filed 2–10–98; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 177

[Docket No. 97N–0301]

Indirect Food Additives: Polymers

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the food additive regulations for Nylon 6/66 resins to change the melting point range from 380–400 °F to 380–425 °F. This action is in response to a petition filed by Ube Industries (America), Inc.

DATES: Effective February 11, 1998; written objections and requests for a hearing by March 13, 1998.

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

FOR FURTHER INFORMATION CONTACT: Vir D. Anand, Center for Food Safety and Applied Nutrition (HFS–215), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202–418–3081.

SUPPLEMENTARY INFORMATION: In a notice published in the **Federal Register** of July 21, 1997 (62 FR 39003), FDA announced that a food additive petition (FAP 7B4548) had been filed by Ube Industries (America), Inc., c/o Center for Regulatory Services, 2347 Paddock Lane, Reston, VA 20191. The petition proposed to amend the food additive regulations in § 177.1500 *Nylon resins* (21 CFR 177.1500), for Nylon 6/66 resins described in the table in paragraph (b), entry 4.2, to change the melting point range from 380–400 °F to 380–425 °F.

The filing notice for the petition (62 FR 39003) stated that the action resulting from the petition qualified for a categorical exclusion under previous 21 CFR 25.24(9). This was a misprint and should have cited 21 CFR 25.24(a)(9). Upon further review, the agency determined that such a categorical exclusion, which is based on a technical change in a regulation, is not appropriate for this proposed action because the proposed amendment is not simply a technical change. Consequently, the agency considered the environmental effects of this action.

FDA has evaluated data in the petition supporting the chemical identity of the additive and other relevant material. The agency finds that the petitioner has adequately demonstrated that Nylon 6/66 with a melting point that includes the range from 400–425 °F meets the specifications under § 177.1500(b), entry 4.2. Based on this information the agency concludes that: (1) The proposed use of the additive is safe, (2) the additive will achieve its intended technical effect, and that therefore, (3) the regulations in § 177.1500 should be amended as set forth below.

In accordance with § 171.1(h) (21 CFR 171.1(h)), the petition and the documents that FDA considered and relied upon in reaching its decision to approve the petition are available for inspection at the Center for Food Safety and Applied Nutrition by appointment with the information contact person listed above. As provided in § 171.1(h), the agency will delete from the documents any materials that are not available for public disclosure before making the documents available for inspection.

The agency has carefully considered the potential environmental effects of this action. FDA has concluded that the action will not have a significant impact on the human environment, and that an environmental impact statement is not required. The agency's finding of no significant impact and the evidence supporting that finding, contained in an environmental assessment, may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday.

Any person who will be adversely affected by this regulation may at any time on or before March 13, 1998, file with the Dockets Management Branch (address above) written objections thereto. Each objection shall be separately numbered, and each numbered objection shall specify with particularity the provisions of the regulation to which objection is made and the grounds for the objection. Each numbered objection on which a hearing is requested shall specifically so state. Failure to request a hearing for any particular objection shall constitute a waiver of the right to a hearing on that objection. Each numbered objection for which a hearing is requested shall include a detailed description and analysis of the specific factual information intended to be presented in support of the objection in the event that a hearing is held. Failure to include such a description and analysis for any particular objection shall constitute a waiver of the right to a hearing on the objection. Three copies of all documents shall be submitted and shall be identified with the docket number found in brackets in the heading of this document. Any objections received in response to the regulation may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 177

Food additives, Food packaging.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs and redelegated to the Director, Center for Food Safety and Applied Nutrition, 21 CFR part 177 is amended as follows:

PART 177—INDIRECT FOOD ADDITIVES: POLYMERS

1. The authority citation for 21 CFR part 177 continues to read as follows:

Authority: 21 U.S.C. 321, 342, 348, 379e.

§ 177.1500 [Amended]

2. Section 177.1500 *Nylon resins* is amended in the table in paragraph (b) for entry ''4.2'' under the heading ''Melting point (degrees Fahrenheit)'' by removing ''380–400'' and adding in its place ''380–425''.

Dated: January 30, 1998.

Janice F. Oliver,

Acting Director, Center for Food Safety and Applied Nutrition.

[FR Doc. 98–3356 Filed 2–10–98; 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: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its regulations pertaining to new drug applications (NDA's) to clearly define in the NDA format and content regulations the requirement to present effectiveness and safety data for important demographic subgroups, specifically gender, age, and racial subgroups. FDA

also is amending its regulations pertaining to investigational new drug applications (IND's) to require sponsors to tabulate in their annual reports the numbers of subjects enrolled to date in clinical studies for drug and biological products according to age group, gender, and race. This action is intended to alert sponsors as early as possible to potential demographic deficiencies in enrollment that could lead to avoidable deficiencies later in the NDA submission. This rule does not address the requirements for the conduct of clinical studies and does not require sponsors to conduct additional studies or collect additional data. It also does not require the inclusion of a particular number of individuals from specific subgroups in any study or overall. The rule refers only to the presentation of data already collected.

DATES: Effective August 10, 1998. Submit written comments on the information collection provisions of this final rule by April 13, 1998.

ADDRESSES: Submit written comments on the information collection provisions of this final rule to the Dockets Management Branch (HFA–305), 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 301–827–6197.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of September 8, 1995 (60 FR 46794), FDA proposed to amend its NDA regulations at § 314.50(d)(5) (21 CFR 314.50(d)(5)) to require sponsors of NDA's to include in their applications analyses of effectiveness and safety data for important demographic subgroups, specifically gender, age, and racial subgroups and, as appropriate, other subgroups of the population of patients being treated, such as patients with renal failure or patients with different severity levels of the disease. This action codifies expectations that FDA has described in previous guidance. FDA also proposed to amend its IND regulations at § 312.33(a)(2) (21 CFR 312.33(a)(2)) to require IND sponsors to characterize in their annual reports the numbers of subjects enrolled in a clinical study for a drug or biological product according to age group, gender, and race.

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 also is 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 (e.g., pediatrics, geriatrics, patients with renal failure) * * * [and] an integrated summary of all available information about the safety of the drug product * * *. However, as discussed in section I of this document, a review of various agency studies and examinations of NDA data bases has revealed that in many cases (about half) data collected and submitted as part of an NDA still are not being analyzed consistently to look for differences in response to drugs among various population subgroups.

This final rule reflects the growing recognition within the agency and the health community that: (1) Different subgroups of the population may respond differently to a specific drug product and (2) although the effort should be made to look for differences in effectiveness and adverse reactions among such subgroups that effort is not being made consistently.

Since the early 1980's, FDA has been concerned about possible differences in response to drugs among subsets of the overall population, such as age, gender, or racial subsets. The agency has addressed in various ways the question of how to obtain information that would permit individualization of therapy. Evaluation of potential differences among demographic subsets requires that individuals from these subsets be included in studies and that analyses to seek differences in response be carried out. During the past decade, FDA has encouraged demographic subgroup analyses in various guidance documents and other regulatory actions. FDA also has examined the extent of participation of patient subgroups in drug development programs.

In 1983 and again in 1989, FDA examined the relative numbers of individuals in NDA data bases from two important demographic subgroups, women and the elderly (58 FR 39406 at 39412, July 22, 1993). 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 agency also found that, in general, the elderly were reasonably well represented in clinical trials.

In a study of drugs approved during the period 1988 through 1991, conducted by the General Accounting Office (GAO) entitled ''FDA Needs to Ensure More Study of Gender Differences in Prescription Drug Testing,'' GAO/HRD–93–17, 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. Analysis also showed that, even when enough women are included in testing, trial data often are not analyzed to determine if women's responses to a drug differed from those of men. The study also showed that the participation of women took place primarily during the later phases of drug development.

FDA's first formal encouragement to analyze population subsets appeared in the 1985 version of § 314.50, in which paragraph (d)(5)(v) (integrated summary of effectiveness) called for evidence to support modifications of dosage for specific subgroups, e.g., pediatrics, geriatrics, patients with renal failure. In 1988, the agency developed the ''Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications'' to explain aspects of the 1985 revision of § 314.50. In that guidance, FDA discussed the importance of analyzing data from population subsets within NDA data bases to look for differences in effectiveness and adverse reactions to drugs. The guidance addressed the importance of subgroup analyses of both safety and effectiveness and of analyses in subgroups other than those mentioned in the regulations.

In 1989, after several years of public discussion, the agency addressed the need to develop information on the elderly in a guideline entitled ''Guideline for the Study of Drugs Likely to be Used in the Elderly.'' The guideline provides guidance regarding the inclusion of elderly patients in clinical trials and the assessment of clinical and pharmacokinetic differences between older and younger patients. In addition, the agency issued a final rule in the **Federal Register** of August 27, 1997 (62 FR 45313), entitled ''Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Addition of 'Geriatric Use' Subsection in the Labeling,'' which, among other things, requires the inclusion of a subsection on geriatric use in the labeling of drugs.

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 provides guidance on FDA's expectations regarding including both men and women in drug development, the need to analyze clinical data by gender, the assessment of potential pharmacokinetic differences between genders, and the conduct of specific additional studies in women, where indicated. The 1993 guideline also describes how concerns about the adequacy of data on the effects of drugs in women have arisen within 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.

In 1993, FDA also published guidance on the agency's use of the refusal-to-file (RTF) option. The guidance states that the agency generally can exercise its RTF authority under 21 CFR 314.101(d)(3) if there is ''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 * * *.''

Despite repeated agency encouragement in both regulations and guidance, FDA and GAO have found that the analysis of effectiveness and safety data in relevant population subgroups, including age, gender, and racial subgroups, is not being carried out consistently. This rule makes the need for these subgroup analyses completely clear.

II. Highlights of the Final Rule

This final rule revises current IND annual report regulations at § 312.33(a)(2) to require that the number of subjects entered to date into a clinical study for drug or biological products be tabulated by age group, gender, and race. This action is intended to alert sponsors and the FDA as early as possible to potential demographic deficiencies in enrollment that could lead to avoidable deficiencies in the NDA submission.

The current wording of NDA content and format regulations at § 314.50(d)(5) does not fully reflect the need to present in the NDA the safety and effectiveness data by subgroup. It also omits specific mention of some important subgroups, including those of gender and race. Therefore, this final rule also revises NDA content and format regulations at § 314.50(d)(5) to require that effectiveness and safety data be presented for demographic subgroups including age group, gender, and race and, when appropriate, other subgroups of the population of patients treated, such as patients with renal failure, or patients with different severity levels of the disease.

In response to comments received on the proposed rule, the agency is making minor changes to the wording to clarify the intent of the rule. In § 312.33(a)(2), ''characterized'' has been changed to ''tabulated'' to make clear that the numbers of the subjects enrolled to date in clinical studies need only be counted and listed in tabular form in annual reports according to age group, gender, and race. No analysis of data is being required for annual reports. Some comments asked for clarification of the phrase, ''as appropriate'' in § 314.50(d)(5)(v) and (d)(5)(vi). When data suggest a different response to a drug product in a subgroup other than age group, gender, or race, it is appropriate to present the data for such a subgroup in the NDA. Examples of such subgroups include subjects who seem to respond differently because of a concomitant disease, renal failure, or different severity level of the disease. The agency is changing the phrase ''as appropriate'' to ''when appropriate.'' The phrase ''and shall identify any modifications of dose or dose interval needed for specific subgroups'' has been added to the end of the second sentence in § 314.50(d)(5)(v) to restore wording that was removed in the proposal. The agency believes that the reinsertion of this wording makes the intent of the rule clearer than the proposed wording.

FDA believes this final rule will help focus drug sponsors' attention throughout the drug development process on the enrollment in clinical drug trials of subjects representing the various subgroups of the population expected to use the drug being tested once it is approved and marketed. Although enrollment generally is broad and reflects the population with the disease, this is not always the case. The rule also will help sponsors better evaluate in their NDA's the safety and efficacy profiles of drugs for various subgroups. Because this rule clarifies agency expectations about the analysis of data that should be included in the NDA to evaluate possible differences in response among gender, age, and racial subgroups, an RTF action based on failure to carry out such critical analyses will be less likely.

III. Comments on the Proposed Rule

FDA received 13 comments on the proposed rule, 8 from representatives of pharmaceutical companies and 5 from health professional, pharmaceutical, and special interest associations. Most comments supported FDA's proposal. One comment called it ''a major step forward.'' Another called it ''a catalyst to uncover potential gender-related differences in drug response.'' Others commended the agency for efforts to safeguard public safety by codifying previously announced FDA policy regarding demographic subgroup analyses.

Two comments were less supportive. One comment said that the proposal ''is premature and substitutes the real risk of false positives for the largely theoretical risks of false negatives.'' This comment recommended that the conduct of subgroup analyses be addressed ''in a scientifically driven manner to avoid increasing the expenditure of resources without a clear or likely benefit.'' The other comment said that the proposal is ''relatively meaningless'' as it requires only the reporting of data already collected; if the sponsor has not collected any data relevant to subgroup analysis, the proposed rule will not cure the deficiency. Several comments also raised specific issues for consideration by the agency. The specific issues raised in the public comments are discussed in sections III.A, B, and C of this document.

A. IND Annual Reports

Current IND annual report regulations, at § 312.33(a)(2), require sponsors to include in annual reports 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. FDA proposed to amend § 312.33(a)(2) to require sponsors to characterize the number of subjects entered into the study to date by age group, gender, and race.

1. Three comments opposed the proposal because they felt that presentation of demographic information in IND annual reports would provide little or no useful information and would add an unnecessary layer of bureaucracy and cost to drug development at a time when pending proposals for FDA reform seek to reduce these costs. One comment said that the agency's expectations and policy in this area are well known through guidelines and

would be made more explicit through codification of the proposed amendments to § 314.50(d)(5), but that the proposal to change reporting requirements in IND's would not provide additional assurance that these expectations would be met.

2. Two comments stated that the proposed change to the IND regulations was redundant because of the proposal to evaluate subgroup information in NDA applications. One of the comments requested that FDA limit subgroup reporting to NDA's.

3. Two comments noted that reporting demographic information in IND annual reports would not provide accurate information and could be misleading because early studies would have small numbers of subjects and may not necessarily be representative of the final study population. One of the comments stated that recruitment of sufficient numbers of patients distributed across subgroups is the responsibility of the sponsor and, if necessary, enrollment demographics could be discussed with the FDA at the appropriate stages of development. Another comment said that current regulations require IND sponsors to submit a clinical plan that would inform the agency of the sponsor's intentions regarding the inclusion of various subgroups in clinical trials. The comment noted that the agency would not be provided with a complete picture of the overall clinical trial program because many drug development programs include substantial amounts of clinical data from studies conducted outside the United States, which are not necessarily conducted under the IND.

FDA believes that all of these comments reflect a misunderstanding of the intent and scope of the proposed IND amendment. This rulemaking only requires drug sponsors to tabulate the number of subjects enrolled to date in clinical drug trials by demographic subgroup, including age group, gender, and race, to enable sponsors and FDA to track enrollment in clinical trials of members of the various subgroups of the population expected to use the drug once it is marketed. FDA believes that the effort and cost imposed by this requirement will be negligible and that the requirement is important for IND submissions because it will give sponsors an early warning of a possible significant deficiency in the developing data base that could lead to avoidable deficiencies in the NDA submission.

4. One comment requested that FDA only require inclusion of demographic data in IND annual reports after it is available in the clinical data base. The comment noted that, when patient case records are still in the field, demographic information would not be available in a ''verifiable'' form.

FDA declines to revise the proposed amendment to limit the submission of demographic information in IND annual reports to data in clinical data bases because, in most cases, much of the required demographic data already will be available upon subject enrollment. The amendment does not require that the data be absolutely verifiable prior to reporting. The agency emphasizes that this amendment is not intended to change information-gathering methods. It only requires the tabulation of available demographic data on the participants enrolled in clinical drug trials.

5. Four comments addressed the conduct of subgroup analyses in IND annual reports even though FDA had not proposed to require such analyses. One comment said that it would be unproductive and burdensome to split summarized data in IND annual reports into subgroups because data in these reports already have little power. Another comment assumed that safety and efficacy of individual subgroups need not be demonstrated while one other comment requested that FDA clearly state that this assumption is true. These comments requested that FDA state that statistical demonstration of subgroup safety and efficacy would be required only if a claim is being made relative to the subgroup. One of the comments also requested that FDA state that a lack of significant findings in a subgroup would not be adversely reflected in the labeling. Another comment said that subgroup analyses may pose special problems because IND annual reports are sometimes prepared using interim data bases that contain data intended for a variety of purposes that may, or may not, include those identified in the proposal.

FDA emphasizes that this rule only requires the tabulation in IND annual reports of the numbers of subjects enrolled to date by demographic subgroups, including age group, gender, and race. FDA believes that it is important to tabulate demographic information in IND annual reports to track the enrollment of subjects representing those who are expected to use the drug product. 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. As a result, this rule does not require analysis of subgroup data in IND annual reports.

6. One comment requested that FDA require a sponsor to file gender accrual data *and* analyze the data in IND annual reports. The comment noted that on January 19, 1995, the National Task Force on AIDS Drug Development recommended conducting gender accrual analysis in IND annual reports. The comment pointed out that under the proposal such an analysis would not be required if subgroup data did not exist and, if available, would yield a very limited and inaccurate gender accrual analysis. The comment also noted that, from a scientific perspective, use of the data thus far collected would most likely result in a statistically skewed by-gender analysis.

FDA declines to revise the proposed amendment to require the analysis of subgroup data in IND annual reports. The final rule requires only that the number of subjects be tabulated by age group, gender, and race in annual reports to alert drug sponsors to potential demographic deficiencies in their enrollment. The rule does not require an analysis of such data at this stage in drug development.

B. NDA Content and Format

FDA proposed to revise the requirements for the content and format of NDA's, under § 314.50, to require sponsors to submit effectiveness (§ 314.50(d)(5)(v)) and safety (§ 314.50(d)(5)(vi)(*a*)) data by gender, age, and racial subgroups and, as appropriate, other subgroups of the population of patients to be treated, such as patients with renal failure or patients with different severity levels of the disease.

7. Two comments supported these amendments when they pertained to NDA integrated summaries of efficacy and safety, but did not support their inclusion in individual study reports. The comments noted that the integrated summaries of safety and efficacy are the most appropriate place for subgroup analyses because the full NDA data base provides sample sizes that can more likely withstand such analyses and also allows an evaluation of consistency of effects across studies. One of the comments said that subgroup analyses in individual study reports would increase bulk and add nothing to the evaluation of either safety or efficacy because, in isolation, these analyses can be misleading at worst and at best amount to needless replication of results that still need to be presented in context, i.e., in light of other relevant studies. The comment requested that FDA revise proposed § 314.50(d)(5)(v) by adding the following sentences: ''These gender, age, and racial subgroup summaries (and, when appropriate, other subgroup summaries) should be

based on all parts of the NDA database that are relevant to the efficacy of the drug product in those subgroups. Therefore, in general, the appropriate place for these subgroup analyses will [be] in the Integrated Summary of Efficacy (rather than in individual study reports).'' The comment proposed similar language for safety data, under proposed § 314.50(d)(5)(vi)(*a*).

FDA agrees that the most appropriate place for the conduct of subgroup analyses in an NDA is in the integrated summaries of effectiveness and safety. This is why the agency is codifying the requirement for subgroup summaries under the paragraphs of the clinical data section of the format and content requirements that pertain to the integrated summary of effectiveness (§ 314.50(d)(5)(v)) and safety (§ 314.50(d)(5)(vi)(*a*)).

FDA declines, however, to add language saying that, in general, it *is* inappropriate for sponsors to conduct subgroup analyses in individual study reports because sometimes it is useful to conduct such analyses. The 1988 ''Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications,'' the 1989 ''Guideline for the Study of Drugs Likely to be Used in the Elderly,'' and the 1993 ''Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs'' advise sponsors to carry out subset analyses that consider the entire efficacy and safety data bases (i.e., in integrated summaries), but also suggest that, if individual studies are large enough, it may be useful to consider subsets in individual studies. Even in integrated summaries, subset analyses may be based on pooled data or may examine subset results by looking at the range of results in individual studies. FDA recognizes that although the analysis of subsets with particular characteristics in individual studies often detects only relatively large differences, such differences could be useful in suggesting hypotheses worth examining in other studies and help refine labeling information, patient selection, dose selection, and other information.

To better clarify the requirement for subgroup summaries for effectiveness data, FDA changed proposed § 314.50(d)(5)(v) by adding a phrase, ''and shall identify any modifications of dose or dose interval needed for specific subgroups,'' to the end of the second sentence in paragraph (v). The phrase ''and modifications for specific subgroups'' had been removed in the proposed amendment. The reinsertion of similar wording makes it clear that one important reason for presenting effectiveness data by age group, gender, and race is to identify any modifications of dose or dose interval that might be needed for those subgroups.

8. One comment contended that the proposal requires data to be presented by subgroups without a clear rationale. The comment suggested that sponsors use a screening hypothesis test in the integrated summaries to see if groups are behaving differently or provide summary information by appropriate subgroups to look for trends. The comment requested that FDA require sponsors to perform subgroup analyses only when there is a biologically plausible, data-driven reason for concern. The comment indicated that such a scientific approach would result in more appropriate labeling and avoid drawing conclusions from poorly powered data. Another comment asked whether interaction tests (e.g., by-gender treatment) would be acceptable for purposes of exploring whether there are differences among subgroups.

Another comment noted that regulatory misinterpretations regarding compliance could result because some indications are specific to one or more subgroups and FDA personnel, who will be deciding on the appropriate type of analysis, may not be familiar with all indications of the group and subgroup.

Two comments requested that FDA only require analyses of primary or key efficacy and safety variables to allow for a more efficient review and to avoid drawing inferences that lack a statistical basis. One of the comments said that it might be appropriate to perform such analyses only when sample sizes are ''large enough.''

In the ''Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications,'' FDA indicates that examination of subsets need not routinely involve formal statistical analysis. In comparisons of safety and effectiveness results in subsets, differences of clinically meaningful size are of interest. If these are not observed, the minor differences that are an expected consequence of random variation should be displayed, but need not be analyzed further and would not ordinarily appear in labeling. This guideline reflects current FDA perspectives on the importance of subgroup evaluations and should provide the guidance requested by the comments.

9. One comment requested clarification of the proposed phrase ''as appropriate.'' The comment asked whether ''other subgroups'' would be determined by or discussed with the FDA on a case-by-case basis for each clinical trial or clinical trial setting.

For clarity, FDA has changed the phrase ''as appropriate'' to ''when appropriate.'' FDA advises that the phrase ''when appropriate'' means: When a subset of the population can be identified that might require a modification of dosing to ensure safe and effective administration of the drug product, it is appropriate to present an analysis of data for that subgroup. In particular, sponsors should consider subgroups for whom the metabolism or excretion of the drug might be altered, e.g., patients with renal or hepatic, or cardiac failure, or patients with different severity levels of the disease. The sponsor may request advice on this matter from the division responsible for review of their application.

C. General

10. Many comments questioned the extent to which the proposal would affect clinical trial design because they believed that the proposal could lead to a request for subgroup sample sizes that are adequate to interpret results. One comment noted that an RTF action could result if a clinical trial does not yield sufficient dosing data for each gender, for every racial subgroup, and for every age group of patient that may be treated. Another comment asked whether the National Institutes of Health (NIH) ruling of 1993, which calls for ''sufficient numbers to allow valid analyses,'' would affect the proposal. The comment asked whether larger trials would be required to adequately power subgroup analyses, or, if subgroup differences are shown to be descriptively or statistically significant, would additional studies be required to confirm or explain the results. The comment noted that statistically significant differences found in ad hoc statistical hypothesis testing could yield a high false-positive rate.

Another comment asked whether subsets were more or less important than centers because it has been their practice to attempt to achieve balance in the assignment of treatment arms in clinical trials by center.

One comment requested clarification of the following phrases discussed in the preamble to the proposed rule (60 FR 46795): ''There must be an effort to use the data to discover such [subgroup] differences'' and ''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.''

Another comment requested clarification of the phrase ''[the] rule refers only to the presentation of data already collected.''

Another comment said that the proposed reporting requirement to ''characterize'' the number of subjects in a clinical study according to age group, gender, and race is inconsistent with the statement in the proposal that it does ''not require sponsors to conduct any more studies than they have already conducted.''

One comment requested that FDA revise the statement to clarify that the rule's criteria can be met by enhanced analysis of existing data.

One comment requested that FDA require sponsors who do not have data pertaining to the differences of the investigational new drug's effects by gender to conduct additional studies to obtain such data. The comment contended that the proposal appears to be an empty gesture because it requires nothing more than a report of numbers and would not cure the lack of knowledge about how drugs affect women. The comment also requested that FDA require sponsors to assess potential differences between genders including a record of side effects or treatment response differences and appropriate pharmacokinetic and pharmacodynamic data as well as a report on hormonal influences. The comment indicated that, if a sponsor has such data, it can be used to predict when specific interactions are important.

The agency believes that all of these comments reflect a misunderstanding of the intent and scope of the proposed amendments. This rule does not require any change in the number of studies a drug sponsor needs to conduct, nor does it impose any new requirements on the conduct of those studies. The rule refers only to the presentation of data that already have been collected. FDA's expectations for inclusion of subgroups in clinical trials and analysis of data generated from such groups are described in FDA guidelines entitled ''Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications,'' ''Guideline for the Study of Drugs Likely to be Used in the Elderly,'' and ''Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs''. This rule does not affect those recommendations.

In the ''Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications,'' FDA recommends analyzing NDA data to identify variations among population subsets in favorable responses (effectiveness) and unfavorable responses (adverse reactions) to drugs. The population subsets that should be evaluated routinely include demographic subsets, such as different age groups, genders, and races; people receiving other drug therapy; and people with concomitant illness. The guideline refers only to the analyses needed. It does not address the question of what the extent of drug exposure (number of patients) of any particular subset of the population should be.

The ''Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs'' does set forth recommendations for subgroup enrollment. The guideline states that sponsors are expected to enroll a full range of patients in their studies; carry out appropriate analyses to evaluate potential subset differences in the patients they have studied; study possible pharmacokinetic differences in patient subsets; and carry out targeted studies to look for subset pharmacodynamic differences that are especially probable, that are suggested by existing data, or that would be particularly important if present. In general, the patients included in clinical studies should reflect the population that will receive the drug when it is marketed. Although it may be reasonable to exclude certain patients at early stages because of characteristics that might make evaluation of therapy more difficult (e.g., patients on concomitant therapy), such exclusion should be abandoned as soon as possible in later development so that possible drug-drug and drug-disease interactions can be detected. The guideline also describes specific guidance for gender-related studies. The ''Guideline for the Study of Drugs Likely to be Used in the Elderly'' likewise provides specific guidance for age-related studies in the elderly.

11. A number of comments requested that FDA provide definitions for subgroups. Two comments requested a definition for the age categories to avoid the potential need to rework existing data. One of the comments suggested that FDA consider the following subgroups for the pediatric population: Newborns (birth to 3 months), infants (3 months to 2 years), children (2 to 12 years) and adolescents (12 to 18 years). The comment requested that FDA require that all available safety, pharmacokinetic, and efficacy data be presented for each of these subgroups. One comment requested that FDA define subpopulations of women. The comment indicated that safety, pharmacokinetic, and efficacy data for pregnant women should be presented separately from data for women who are not pregnant. Two comments requested that FDA define categories for race. One of the comments noted that it may be somewhat problematic to implement the proposal because race descriptions used in the United States may not be appropriate in other countries.

In its final rule on the revision of the pediatric use subsection in labeling (59 FR 64240, December 13, 1994), FDA offered the following guidance for defining the pediatric population: (1) Birth to 1 month (neonates), (2) 1 month to 2 years of age (infants), (3) 2 years to 12 years (children), and (4) 12 years to 16 years (adolescents). Where possible, data should be analyzed according to these groups. Alternatively, it usually would not be necessary to establish a drug product's effectiveness in each group. On the other hand, it may be important to have some pharmacokinetic information in each group, especially the younger age groups, to guide dosing and additional information, such as a specific study in neonates, to establish safety.

In the final rule on geriatric labeling (62 FR 45313 at 45316, August 27, 1997), the agency defined ''elderly'' as persons aged 65 years and over. FDA recommends that sponsors use this definition for analysis of data for the elderly population.

FDA declines to define subpopulations of women because it is not necessary. Usually, pregnant women would only participate in clinical trials intended specifically to study drug effects during pregnancy. The data generated from such trials would, therefore, reflect use in this subpopulation of women.

FDA also does not believe it necessary to define specific racial categories in this rule because drug sponsors have been very successful thus far in identifying the relevant racial categories to help them examine safety and efficacy profiles of drugs in relation to race and to identify potential metabolic differences in accordance with race that could have important biomedical implications. Because of the diversity of the U.S. population, the changing racial composition of the population, and the sensitivities of categorizing individuals according to race, FDA recommends that sponsors use the approach common in such efforts to capture demographic data, by asking subjects in clinical trials to identify their racial group. If they desire, sponsors may use the categories and definitions offered in The Office of Management and Budget (OMB) Directive No. 15, which currently identifies the following racial groups:

American Indian or Alaskan Native: A person having origins in any of the original peoples of North America.

Asian or Pacific Islander: A person having origins in any of the original peoples of the Far East, Southeast Asia, the Indian subcontinent, or the Pacific Islands. This area includes, for example, China, India, Japan, Korea, the Philippine Islands, and Samoa.

Black: A person having origins in any of the black racial groups of Africa.

White: A person having origins in any of the original peoples of Europe, North Africa, or the Middle East.

Many subjects may choose to identify their race as Hispanic, which can include a person of Mexican, Puerto Rican, Cuban, Central or South American or other Spanish culture or origin, regardless of race. Technically, however, the term ''Hispanic'' is used to describe an ethnic, rather than a racial, group.[1]

12. One comment requested that FDA ensure that the proposal is consistent with International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) initiatives, in particular, Topic E3: Structure and Content of Clinical Reports. The comment noted that such consistency is important for global harmonization.

FDA notes that the final rule is consistent with ICH initiatives. In the **Federal Register** of July 17, 1996 (61 FR 37320), FDA issued an ICH guideline entitled ''E3 Structure and Content of Clinical Study Reports.'' This guideline recommends that an individual clinical study report describe demographic characteristics of the study population and, where the study is large enough to permit this, present data for demographic and other subgroups (e.g., renal or hepatic function) so that possible differences in efficacy or safety can be identified. The guideline also notes that subgroup responses usually should be examined in the larger data base used in the overall analysis. This is the only ICH guideline to date that contains information relevant to this final rule.

13. One comment requested that FDA describe how the proposal will be implemented. The comment suggested that it be implemented on an incremental basis, especially with regard to the required changes in content and format of submissions and the required updates. The comment noted that it is important to publicize the timing and effective date of the rule prior to enforcement. Otherwise, the comment contended, it could cause an enormous burden and expense to sponsors and manufacturers. The comment also requested that FDA state its position on the subject of retroactivity, i.e., when the agency would require reports to be changed and how much advance notice the agency would give.

FDA is requiring that this final rule become effective on August 10, 1998. All IND annual reports and NDA applications submitted to the agency on or after the effective date must be in the format specified in the final rule. FDA believes that this period of time is sufficient for preparation of these documents because the final rule does not change information-gathering methods nor does it require sponsors to conduct additional studies or collect additional data. The final rule codifies expectations that the agency has described in previous guidance regarding the presentation of data already collected.

14. One comment suggested that FDA consider sponsorship of an educational forum such as a workshop or an interactive telecast (e.g., FDA/Food and Drug Law Institute telecast) to inform sponsors of the new regulations.

At present, FDA is not planning a workshop or interactive telecast on this subject, but may consider sponsoring one if sufficient interest exists. FDA will make information regarding this rule available on its World Wide Web site at http://www.fda.gov/cder/guidance.htm. Interested persons may submit requests for a workshop or interactive telecast to the Dockets Management Branch (address above) under Docket No. 95N–0010.

IV. Environmental Impact

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

V. Paperwork Reduction Act of 1995

This final rule contains information collection provisions that are subject to review by OMB under the Paperwork Reduction Act of 1995 (the PRA of 1995) (44 U.S.C. 3501–3520). The title, description, and respondent description of the information collection provisions are shown below with an estimate of the annual reporting and recordkeeping burdens. Included in the estimate is the time required for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

Title: Presentation of Safety and Effectiveness Data for Certain Subgroups of the Population in Investigational New Drug Application Reports and New Drug Applications.

Description: This final rule amends the new drug application format and content regulations to require the presentation of effectiveness and safety data for important demographic subgroups, specifically gender, age, and racial subgroups and, when appropriate, other subgroups of the population of patients being treated, such as patients with renal failure or patients with different severity levels of the disease. The final rule also amends FDA's regulations pertaining to IND's to require sponsors to tabulate in their annual reports the numbers of subjects enrolled to date in clinical studies for drug and biological products according to age group, gender, and race. This action is intended to alert sponsors as early as possible to potential demographic deficiencies in enrollment that could lead to avoidable deficiencies later in the NDA submission.

This rule does not address the requirements for the conduct of clinical studies and does not require sponsors to conduct additional studies or collect additional data. It also does not require the inclusion of a particular number of individuals from specific subgroups in any study or overall. The rule refers only to the presentation of data already collected.

The data required to be presented under this final rule will assist the sponsor and the agency in monitoring the enrollment in clinical drug trials of subjects representing various subgroups of the population expected to use the drug once it is approved and marketed. The data also will help the sponsor and the agency to evaluate the safety and efficacy profiles of drugs for various subgroups.

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

Although the proposed rule of September 8, 1995 (60 FR 46794), provided a 90-day comment period under the PRA of 1980, FDA is providing an additional opportunity for public comment under the PRA of 1995, which became effective after the publication of the proposed rule and applies to this final rule. Therefore, FDA now invites comments on: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether

[1] OMB has proposed adding the ethnic category ''Hispanic'' to Directive No. 15 (62 FR 36874, July 9, 1997).

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, when appropriate, and other forms of information technology. Individuals and organizations may submit comments on the information collection provisions of this final rule by April 13, 1998. Comments should be directed to the Dockets Management Branch (address above).

At the close of the 60-day comment period, FDA will review the comments received, revise the information collection provisions as necessary, and submit these provisions to OMB for review and approval. FDA will publish a notice in the **Federal Register** when the information collection provisions are submitted to OMB, and an opportunity for public comment to OMB will be provided at that time. Prior to the effective date of this final rule, FDA will publish a notice in the **Federal Register** of OMB's decision to approve, modify, or disapprove the information collection provisions. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

TABLE 1.—ESTIMATED ADDITIONAL ANNUAL REPORTING BURDEN[1]

21 CFR Section	Anuual No. of Respondents	Annual Frequency	Average Burden per Respons	Annual Hours
312.33(a)(2)	1,616 (noncommercial)[2]	1	2 hours	3,232
312.33(a)(2)	362 (commercial)	1	8 hours	2,896
314.50(d)(5)	50	1	40 hours	2,000
Total				8,128

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

[2] For purposes of this document, a commercial study under an IND is conducted by a sponsor that is in the process of developing a drug to the point of commercial marketing. A noncommercial study under an IND is sponsored, generally, by government agencies or academic institutions for the purpose of gaining knowledge about the drug. The agency or institution does not own marketing rights for the drug nor is it intended that the marketing rights holder will submit the results for marketing approval.

For the amendments to § 312.33(a)(2), the estimates are based on the average number of IND annual reports that FDA receives annually. For the amendments to § 314.50(d)(5)(v) and (d)(5)(vi)(*a*), the estimates are based on the average number of NDA's FDA receives annually that do not currently include the information that would be required by the final rule. An average of 100 NDA's are submitted to FDA annually. As indicated elsewhere in the final rule, in half of the cases that FDA and GAO examined, the information that would now be required is currently being presented and analyzed, so the additional cost imposed by the rule has been calculated only for the 50 remaining NDA's. In addition, the agency expects that for the most part, a tabular presentation of descriptive statistics, such as the mean change in a parameter for a particular subgroup, will be sufficient. Only occasionally will it be necessary to do more substantive analysis, when the descriptive statistics suggest a significant difference.

VI. Analysis of Impacts

FDA has examined the impacts of the final 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 agency believes that this final rule is consistent with the regulatory philosophy and principles set forth in Executive Order 12866. The final rule does not require a 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 final rule is not a significant regulatory action as defined in Executive Order 12866 and so is not subject to review under the Executive Order.

The final rule amends IND regulations to enable drug sponsors and FDA to monitor the extent to which patient populations that are likely to receive the drug once it is approved are being enrolled and studied. The final rule amends § 312.33(a)(2) to require that the IND annual report include the number of subjects entered into the study ''tabulated by age group, gender, and race.'' The rule does not require any analysis of collected data for the IND annual report.

The rule also amends NDA regulations at § 314.50(d)(5)(v) and (d)(5)(vi) to clearly define in the format and content regulations the requirement to present effectiveness and safety data for important demographic subgroups including age group, gender, race, and when appropriate, other subgroups of the population of patients to be treated. The rule refers only to the presentation of data already collected and codifies recommendations that FDA has made in previous guidance.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Since the rule will not impose significant costs on any affected firm, it will therefore not impose a significant impact on a substantial number of small entities. The agency certifies that the final 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.

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, 21 CFR parts 312 and 314 are amended as follows:

PART 312—INVESTIGATIONAL NEW DRUG APPLICATION

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

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371; 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, tabulated 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.

* * * * *

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: 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 and shall identify any modifications of dose or dose interval needed for specific subgroups. Effectiveness data from other subgroups of the population of patients treated, when appropriate, such as patients with renal failure or patients with different levels of severity of the disease, also shall be presented.

(vi) * * *

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

* * * * *

Dated: February 2, 1998.

William B. Schultz,

Deputy Commisioner for Policy.

[FR Doc. 98–3422 Filed 2–10–98; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 520

Oral Dosage Form New Animal Drugs; Monensin

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the animal drug regulations to reflect approval of two supplemental new animal drug applications (NADA's) filed by Elanco Animal Health, Division of Eli Lilly & Co. The supplemental NADA's provide for transferring the data and information in one NADA into another and withdrawing approval of the vacated NADA. The NADA's provide for use of monensin Type A medicated articles to make a free-choice Type C medicated feed/mineral granules for pastured cattle for increased rate of weight gain.

EFFECTIVE DATE: February 23, 1998.

FOR FURTHER INFORMATION CONTACT: Russell G. Arnold, Center for Veterinary Medicine (HFV–142), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301–594–1674.

SUPPLEMENTARY INFORMATION: Elanco Animal Health, Division of Eli Lilly & Co., Lilly Corporate Center, Indianapolis, IN 46285, is the sponsor of NADA's 95–735 and 119–823, both of which provide for use of a monensin Type A medicated article to make a monensin Type C medicated feed/free-choice mineral granules containing 810 milligrams monensin per pound (1,620 grams monensin per ton) to be fed free-choice to pasture cattle (slaughter, stocker, feeder, and dairy and beef replacement heifers) for increased rate of weight gain (see 21 CFR 520.1448b and 558.355(f)(3)(x)).

Elanco Animal Health, Division of Eli Lilly & Co. filed supplemental NADA's that provide for combining data and information in NADA 119–823 into NADA 95–735 and withdrawing approval of NADA 119–823. Supplemental NADA 95–735 is approved as of November 3, 1997, and the regulations are amended in part 520 (21 CFR part 520) by removing § 520.1448b to reflect the approval.

Approval of the supplemental NADA 95–735 or withdrawal of approval of NADA 119–823 does not require a freedom of information summary because the actions concern a change in status of existing applications and do not change the conditions of use of the products. This change does not affect the product's safety or effectiveness.

The agency has determined under 21 CFR 25.33(a)(1) and (g) that these actions are of a type that do not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

List of Subjects in 21 CFR Part 520

Animal drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs and redelegated to the Center for Veterinary Medicine, 21 CFR part 520 is amended as follows:

PART 520—ORAL DOSAGE FORM NEW ANIMAL DRUGS

1. The authority citation for 21 CFR part 520 continues to read as follows:

Authority: 21 U.S.C. 360b.

§ 520.1448b [Removed]

2. Section 520.1448b *Monensin-mineral granules* is removed.

Dated: January 22, 1998.

Andrew J. Beaulieau,

Acting Director, Office of New Animal Drug Evaluation, Center for Veterinary Medicine.

[FR Doc. 98–3355 Filed 2–10–98; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[DEA No. 173F]

Schedules of Controlled Substances: Placement of Sibutramine Into Schedule IV

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Final rule.

SUMMARY: With the issuance of this final rule, the Acting Deputy Administrator of the Drug Enforcement Administration (DEA) places the substance,