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(j) This amendment becomes effective on September 11, 1997.

Issued in Burlington, Massachusetts, on August 15, 1997.

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[FR Doc. 97-22677 Filed 8-26-97; 8:45 am]

BILLING CODE 4910-13-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 201

[Docket No. 89N-0474]

RIN 0910-AA25

Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Addition of "Geriatric Use" Subsection in the Labeling

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its regulations governing the content and format of labeling for human prescription drug products, including biological products, to include information pertinent to the appropriate use of drugs in the elderly (persons aged 65 years and over) and to facilitate access to this information by establishing a "Geriatric use" subsection in the labeling. The final rule is one of several measures FDA has taken in response to the special concerns associated with prescription drug use in elderly patients. FDA believes that improving access to information that is important to the elderly will facilitate the safe and effective use of prescription drugs in older populations.

DATES: This final rule becomes effective on August 27, 1998. Submit written comments on the collection of information provisions by October 27, 1997. See section IV of this document

for the implementation dates of this final rule for drug classes and drug products.

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

FOR FURTHER INFORMATION CONTACT: Thomas C. Kuchenberg, Center for Drug Evaluation and Research (HFD-7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-5621.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of November 1, 1990 (55 FR 46134), FDA proposed to amend its prescription drug labeling regulations (§ 201.57) to establish in the "Precautions" section a subsection on the use of drugs in elderly or geriatric patients (aged 65 years and over). The final rule requires, in a new "Geriatric use" subsection of prescription drug labeling, that sponsors describe available information pertinent to the appropriate use of drugs in elderly patients. In cases where none of the provisions of the "Geriatric use" subsection are applicable, FDA may permit omission of the subsection or approve an accurate and appropriate alternate statement.

The final rule recognizes the special concerns associated with the geriatric use of prescription drugs and acknowledges the need to communicate important information so that drugs can be used safely and effectively in older patients. The medical community has become increasingly aware that prescription drugs can produce effects in elderly patients that are significantly different from those produced in younger patients. Although both young and old patients can exhibit a range of responses to drug therapy, factors contributing to different responses are comparatively more common among the elderly. For example, elderly patients are more likely to have impaired mechanisms of drug excretion (e.g., decreased kidney function), to be on other medications that can interact with a newly prescribed drug, or to have another medical condition that can affect drug therapy.

Geriatric labeling information is of increasing importance because of the growing proportion of the population that is over 65 years of age, and the significant use of medications by this age group. People over age 65 constitute only 12 percent of the U.S. population, but they consume over 30 percent of the

prescription drug products sold in this country. The elderly are expected to constitute 22 percent of the U.S. population by the year 2030.

The final rule is one of several actions taken by FDA to promote safe and effective prescription drug use in the elderly. FDA has encouraged sponsors to include more elderly subjects, especially those over 75 years of age, in clinical studies. In the **Federal Register** of March 5, 1990 (55 FR 7777), FDA announced the availability of a guideline entitled "Guideline for the Study of Drugs Likely to be Used in the Elderly." The guideline emphasizes FDA's recommendation that drugs should be studied in the full range of patients who will receive them, including the elderly, and that efforts should be made to discover differences in pharmacokinetics related to age, or to conditions associated with age (e.g., decreased renal function, concomitant drugs, concomitant illness), and that clinical data should be analyzed to see whether the drug has different effects, favorable or unfavorable, in the old and young. The guideline provides detailed advice on how to evaluate new drugs in older patients and is intended to encourage routine and thorough evaluation of the effects of drugs in elderly populations so that sufficient information can be provided to physicians. The guideline did not call for, or anticipate, an increase in the number of patients or the number of clinical studies needed to evaluate a new therapy. Patients over 65 years of age already represented a significant portion of study subjects in most cases, based on several FDA surveys. The principal new steps called for were to not exclude the very old, to analyze the data already collected, and to obtain modest additional pharmacokinetic data. Only in special cases (e.g., drugs especially targeted for older patients or where age-related differences or problems are anticipated) were separate studies in the elderly recommended.

In the **Federal Register** of August 2, 1994 (59 FR 39398), FDA published a guideline regarding the use of drugs in geriatric populations entitled "Studies in Support of Special Populations: Geriatrics." The guideline was prepared by the Efficacy Expert Working Group of the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, which is concerned with the harmonization of technical requirements among the European Union, Japan, and the United States. The guideline reflects sound scientific principles for testing drugs in geriatric populations and for submitting

marketing applications to regulatory authorities worldwide. The guideline is consistent with FDA's existing geriatric guideline discussed previously.

II. Highlights of the Final Rule

This final rule furthers FDA efforts to promote safe and effective prescription drug use in the elderly by requiring that information on the safe and effective use of drugs in the elderly be included in labeling, and by specifying a location and format for presenting this information.

A. General Provisions

The final rule establishes, in new § 201.57(f)(10), a "Geriatric use" subsection that provides information on the safe and effective use of drugs in patients aged 65 and older. This subsection of the "Precautions" section of the labeling describes what is known about the effects of a drug in the elderly and lists any limitations, hazards, or monitoring needs associated with geriatric use.

Although FDA encourages further study of drug effects in the elderly, this labeling change is not intended to require additional clinical studies. The "Geriatric use" subsection is intended to establish a place in prescription drug labeling where practitioners can find pertinent information that is already available from clinical experience and investigations. FDA believes that providing this information in a clear and accessible way should promote the safe and effective use of prescription drugs in the elderly.

Section 201.57(f)(10) also states that specific geriatric indications, if any, are to be described in the "Indications and Usage" section, and specific geriatric dosing instructions are to be described in the "Dosage and Administration" section. Additional details about information summarized in the "Geriatric use" subsection may be found in other sections of the labeling, as appropriate.

B. Sources of Information on Geriatric Use

Under § 201.57(f)(10)(ii), the "Geriatric use" subsection is based on all information available to sponsors that is relevant to the use of the drug in elderly patients. The information includes results from controlled studies, both those that are part of a marketing application and those available to the sponsor but not submitted, information gathered from other studies and experience (e.g., adverse drug reaction reports), and pertinent information from well-documented studies obtained from a literature search.

C. Statements on Geriatric Use

Section 201.57(f)(10)(ii) calls for appropriate labeling statements that are based on the information available regarding use of the drug in geriatric populations:

(1) If there have not been sufficient numbers of geriatric subjects involved in clinical studies to determine whether those over age 65 differ from younger subjects in their responses to the drug, and other reported clinical experience has not identified such differences, § 201.57(f)(10)(ii)(A) requires that the labeling state this fact and note that generally the selection of dosage levels for the elderly should proceed with caution, usually starting at the low end of the dosing range.

(2) If sufficient numbers of geriatric subjects have been included in studies (both those in marketing applications and other relevant studies available to the sponsor) to make it likely that a difference in safety and effectiveness between older and younger subjects would have been detected, but no such differences in safety or effectiveness were apparent and no other reported clinical experience identified such differences, § 201.57(f)(10)(ii)(B) requires that the labeling state this fact. The statement must also indicate the percentage of the total number of subjects, or the total number of subjects, in a defined group of clinical studies who were 65 and over and 75 and over.

(3) If evidence from clinical studies and other reported clinical experience available to the sponsor indicates that use of the drug in elderly patients is associated with differences in safety or effectiveness in the geriatric population, or if administration of the drug to the elderly requires specific dosage adjustment or monitoring, § 201.57(f)(10)(ii)(C) requires that the labeling briefly describe these special geriatric conditions and, when appropriate, refer to other labeling sections for more detailed discussions.

D. "Geriatric Use" and Other Labeling Sections

Section 201.57(f)(10)(iii)(A) requires that if specific pharmacokinetic or pharmacodynamic studies of the drug's action were carried out in the elderly, they must be described briefly in the "Geriatric use" subsection and in detail in the "Clinical Pharmacology" section.

The potential for problems stemming from the use of drugs in patients with certain diseases or from interactions between drugs is higher among the elderly because they are more likely to have multiple illnesses requiring multiple drug treatments. Section

201.57(f)(10)(iii)(A) notes that the "Clinical Pharmacology" and "Drug Interactions" sections of the labeling ordinarily contain information on drug-drug and drug-disease interactions. For example, § 201.57(b) requires, in part, that the Clinical Pharmacology section of the labeling contain a concise factual summary of the clinical pharmacology and actions of the drug in humans.

Section 201.57(f)(4)(i), the "Drug Interactions" subsection of the "Precautions" section, includes a requirement that the labeling shall contain specific practical guidance on preventing clinically significant drug/drug and drug/food interactions that may occur in vivo in patients taking the drug, including identification of specific drugs or classes of drugs with which the drug may interact in vivo in patients and a brief description of the mechanism(s) of the interaction.

If the use of a drug in the elderly appears to cause a specific hazard, the hazard must be described in the "Geriatric use" subsection as required under § 201.57(f)(10)(iv), or information about the hazard would be placed appropriately under the "Contraindications," "Warnings," or "Precautions" sections of the labeling, and the "Geriatric use" subsection would refer to those sections. Geriatric labeling, under § 201.57(f)(10)(v), may also include statements reflecting good clinical practice or experience with a particular situation if they would be useful in enhancing the safe use of the drug. As an example, the final rule provides a possible statement for a sedating drug.

E. Renal Function

Geriatric patients are more likely than younger patients to have impaired renal function. Therefore, when it is known that a drug is substantially excreted by the kidney, § 201.57(f)(10)(iii)(B) requires a statement to that effect in the "Geriatric use" subsection, as well as a statement noting that care should be taken in dose selection and that it may be useful to monitor renal function. Renal function may be monitored by calculating creatinine clearance.

F. Alteration or Omission of Geriatric Statements

Although the geriatric statements provided in the final rule will be appropriate for most drug products, there are certain drugs that are not indicated for geriatric use or for which the specified geriatric statements are not needed. In this situation, the sponsor, under § 201.57(f)(10)(vi), must provide reasons for omitting the specific geriatric use information and statements

in § 201.57 and, if appropriate, may propose alternative geriatric language.

FDA may permit omission of a geriatric use statement and permit the use of an alternate statement if FDA determines that the statements described in § 201.57(f)(10)(i) through (f)(10)(v) are inappropriate or not relevant to the drug's labeling and that the alternate statement is accurate and appropriate.

III. Comments on the Proposed Rule

The agency received approximately 60 comments on the proposed rule. The comments came from Congress, prescription drug manufacturers, physicians, professional societies, organizations with special interests in the elderly, the lay public, and others. Most comments agreed with the proposed labeling change, calling it "long overdue," "timely and important," and a "major step" in promoting the safe and effective use of prescription drugs in the elderly.

Many comments expressed the belief that a "Geriatric use" statement in the labeling would result in increased awareness among practitioners and patients and thus enhance the physician's ability to provide quality health care to older patients.

1. While expressing support, some comments reflected confusion about the practical effect of the regulation, recommending such steps as the use of large print, bright ink, and "simple language" to make the labeling more easily read and understood by older patients.

The agency believes these comments misinterpret the intent of this rulemaking. The regulation does not describe information that would be distributed directly to the patient. Rather, the rule amends the "professional" labeling requirements for prescription drugs, commonly referred to as the physician package insert, to require that a "Geriatric use" subsection appear in the "Precautions" section of the package insert. Professional labeling is designed for and directed to physicians and other health care professionals and is required to provide information "under which practitioners licensed by law to administer the drug can use the drug safely and for the purposes for which it is intended * * *" (§ 201.100(c)(1) (21 CFR 201.100(c)(1)).

Although this final rule does not require that written information on geriatric use be distributed directly to elderly patients or establish any print size requirements, the agency expects that it will result in more and better information reaching these patients. The final rule amends the labeling

requirements to give physicians and other health care professionals easier access to more information about geriatric use. A health care community so informed will be better able to deliver superior care and to provide more information on the safe and effective use of prescription drugs to elderly patients.

Because some confusion exists regarding the purpose of this regulation, and as a result of the changes made in response to comments received, FDA has reformatted and redesignated some provisions in proposed § 201.57(f)(10) for this final rule. These changes were made to clarify obligations and options provided in the regulation. Except where specific substantive changes or additions are indicated and were made in response to comments, these changes do not involve changes in the obligations imposed on sponsors by the regulation. FDA has also replaced the word patient with the more appropriate "subject" when referring to individuals participating in clinical studies.

2. Some comments opposed establishing a "Geriatric use" subsection in prescription drug labeling. The comments stated that in communicating drug information to patients, the role of pharmacists and other health care practitioners should be adequate to reduce problems in the elderly, making this labeling change unnecessary.

The agency disagrees. FDA recognizes that pharmacists and other health care practitioners play important roles in communicating information about prescription drug use to elderly patients. However, surveys show that a substantial number of elderly patients fail, in some way, to comply with their prescription drug regimen; and the elderly population is greatly in need of medication counseling and information. Pharmacists and others cannot transmit information they do not have, and information on how younger and older patients respond differently to a drug is difficult to find.

The final rule does not diminish the role that health care professionals play in communicating information to the elderly about their prescription drugs. Rather, it facilitates that role by providing health care professionals with more information about how drugs affect older patients.

3. One comment claimed that the proposed "Geriatric use" subsection is redundant because existing FDA guidelines and labeling regulations already provide that important information should be included in the labeling.

FDA acknowledges that some prescription drug labeling consistent with existing FDA guidelines and

regulations contains information on use in the elderly. This reflects growing recognition of the need to provide patient information on individualizing drug therapy and, specifically, of the need to provide information on use in the elderly.

The final rule is intended to make geriatric labeling format and content more consistent by requiring that there be a "Geriatric use" statement in prescription drug labeling, that the statement reflect all information available to the sponsor that is relevant to the appropriate use of the drug in elderly patients, that the information, or direct reference to it, be found in a particular location in the labeling, and that the statement follow a standard format. The "Geriatric use" statement will give practitioners and others easier access to more information about prescription drug use in elderly patients.

4. Other comments objected to a "Geriatric use" subsection on economic grounds, saying that the costs of producing and compiling the information necessary to comply with this labeling change will be significant, adding to the already high cost of drug development. The comments were concerned that these costs would be passed along to the elderly consumer, who may not be able to afford them.

The agency's review of the cost issues posed by the comments is contained in section VI of this document. The agency agrees that manufacturers will incur some costs as a result of this final rule. The agency believes, however, that the costs associated with the final rule will not be significant, especially in light of the potential benefits of the labeling change. This rule does not require any new clinical studies, but the preparation of the "Geriatric use" subsection should include analyses of previously collected data and available literature.

The cost of preparing the "Geriatric use" subsection may be offset by lower health care costs resulting from fewer adverse reactions to prescription drugs. Because older people take about three times as many prescription drugs as younger individuals and because taking several drugs together substantially increases the risk of drug interactions, unwanted effects, and adverse reactions (Ref. 1), labeling addressing this information should result in fewer adverse reactions. A number of studies have indicated that adverse drug reactions and patient noncompliance contribute to costly emergency room and hospital visits (Ref. 2). If the information required by the rule prevents only a modest fraction of these

adverse reactions, the health care savings will be sizeable.

Costs will also be lessened by the manner in which the rule is to be implemented. The extended period allotted for implementation is designed to reduce burdens for both industry and the agency. Implementation will take place over 6 years (in accordance with the plan described in section IV of this document). The implementation schedule divides drug products subject to this regulation into four multiyear groups based on the date of approval of the products' new molecular entities (NME's). FDA recognizes that it will be more difficult to develop geriatric labeling for older NME's, due to the probable need to manually examine data and the likelihood that a more extensive literature search will be needed. In contrast, the information available for recently approved drugs is more likely to be readily available to sponsors and more likely to be computer accessible. As a result, implementation will proceed in reverse chronological order.

In addition, the agency will not require prior approval of labeling changes for drug products under § 201.57(f)(10)(ii)(A) (i.e., where insufficient data exist to determine whether the responses of geriatric patients to a drug are different from responses of younger patients).

5. Some comments found the proposed regulation "confusing" and suggested that FDA provide "model labeling" for each drug or drug class.

The regulation does provide specific "model" language for several possible labeling statements. The agency has revised proposed § 201.57(f)(10) to make the "Geriatric use" labeling requirements clearer and to make several organizational and other general changes. The agency does not agree, however, that it should draft model geriatric labeling for each drug or drug class. The agency does not believe that a small number of "models" could be developed that would be helpful in formulating the labeling of all drug products, nor does the agency have the resources necessary to draft such labeling.

6. Several comments objected to the agency's designation of 65 years and older as the age range to which this rule would apply. Some comments called the choice "arbitrary," noting that, while 65 years old has become widely used as a sociological marker of the beginning of senior citizen status, there is no physiological basis for identifying 65 years old as the age at which differences in drug effects begin to occur.

One comment suggested that the age be lowered to include persons in their fifties; others suggested that the appropriate age should be 60 years old; another thought 80 years and older would be the most meaningful age category with regard to differences in drug response. Several comments complained that the proposed rule treated all persons over 65 years old as a homogeneous group, and suggested that it be changed to categorize 65 to 74, 75 to 84, and 85 years and older as three distinct age categories for purposes of assessing drug response.

Other comments suggested that age not be used at all to define the geriatric population, but that other factors, such as changes in body composition or organ function, be used as criteria for categorizing appropriate labeling statements.

The agency recognizes that attempts to define populations to which clinical or regulatory requirements apply are subject to certain limitations and are difficult to achieve. This is evidenced by the number and variety of suggestions for alternative age designations posed by the comments. Nonetheless, for ease of implementation, it is necessary to specifically and simply define the population to which this final rule applies.

Defining the geriatric population based on age (persons 65 years of age and older) lends an important element of uniformity in the development of the "Geriatric use" subsection and establishes boundaries for the application of the final rule. These boundaries are necessary to enable manufacturers to determine how to gather, evaluate, and communicate geriatric use information. Defining the scope of the final rule in this way also will aid practitioners who consult the "Geriatric use" subsection, allowing them to presume that, unless otherwise stated, the population being addressed is 65 years of age and older and that this standard remains constant in all prescription drug labeling. The agency notes that age 65 is a widely used marker for the beginning of elderly status and believes that 65 years of age is a reasonable starting place for a discussion of differences in drug response that are related to advancing age. However, the agency does not consider 65 years of age to be an absolute boundary for this rulemaking. For some drugs, it may be more appropriate for the labeling to reflect evaluation of another elderly age group, or, where there are important differences in response, to address specific subgroups within the geriatric

population. In some cases, changes might be expressed as a continuous function of age. FDA would expect the manufacturer to advise the agency of these cases, and to submit, as appropriate, "Geriatric use" labeling that reflects and communicates these special concerns.

FDA agrees with the comments that note that the interaction of drug responses and the aging process can vary widely among individuals. As with labeling for any age group, "Geriatric use" labeling is no substitute for the sound medical judgment of the prescriber, who must keep in mind individual responses to drug therapy.

7. Several comments questioned the scope of the review a manufacturer would have to undertake to obtain all "available information," as described in the preamble to the proposed rule. The comments claimed that the required review would be too broad in scope, impossible to complete, and would yield irrelevant or useless information. In particular, the comments objected to the use of information obtained from FDA's Spontaneous Reporting System (now the Medical Products Reporting Program or MedWatch) for adverse drug events as the basis of labeling statements, and suggested excluding it from the scope of review. Specifically, these comments requested that the evaluation reflect information from the following: (1) All controlled, clinical trials contained in the new drug application; (2) other controlled, clinical trials in the applicant's possession that are reasonably relevant to the use of the drug in older patients; (3) postmarketing studies or published literature that specifically concern the use of the drug in older patients; and (4) pharmacokinetic and pharmacodynamic studies that have been conducted in the elderly.

The agency has considered the scope of "available information" in light of the recommendations made in these comments. Aside from the suggestion that MedWatch information not be required, the comments support the same review of information as set forth in the proposal. In order for "Geriatric use" labeling to be a meaningful prescribing tool, it must reflect a comprehensive review of a broad range of information sources. The agency believes that the scope of the review appropriately includes information both in the applicant's possession and available through a search of professional literature or published studies that are relevant to an evaluation of the geriatric use of the drug.

Concerning the inclusion of MedWatch information, FDA regards a

review of information from this system or from the Vaccine Adverse Events Reporting System (VAERS) for vaccines as potentially important in developing comprehensive labeling for the safe and effective use of the drug in the elderly. The agency fully appreciates the limitations associated with MedWatch and VAERS data, but believes that this information when placed in its proper context can in some cases yield data on the age-relatedness of adverse effects that are interpretable and valuable. In submitting "Geriatric use" information, a manufacturer should evaluate the merit of particular MedWatch reports and utilize them appropriately.

8. Several comments argued that the proposed "Geriatric use" labeling subsection does not adequately address problems that are frequently associated with prescription drug use in the elderly. The comments contended that the labeling statements should discuss the issue of polypharmacy in the elderly and include specific information on drug-drug interactions. Another comment asserted that the rule overlooks the development of "drug allergies" and the "psychological effects" of prescription drugs in older patients.

The agency believes that the final rule adequately addresses the problems most commonly associated with prescription drug use in the elderly, including those areas cited in the comments. Section 201.57(f)(10)(ii)(C) directs that differences in safety or effectiveness of a drug in the elderly, or specific monitoring or dosage adjustment requirements, shall be described briefly in the "Geriatric use" subsection and, as appropriate, be discussed in more detail in the appropriate section of the labeling. In addition, as stated in § 201.57(f)(10)(iii)(A), data about drug-disease and drug-drug interactions are ordinarily included in the "Clinical Pharmacology" section (§ 201.57(b)) and "Drug interactions" subsection of the "Precautions" section (§ 201.57(f)(4)(i)), and this information is often particularly relevant to the elderly.

9. Other comments expressed concern that the overall approach of the prescribed "Geriatric use" statements is too general and overly cautious. In particular, these comments objected to language in proposed § 201.57(f)(10)(ii)(A), advising that " * * * [i]n general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range * * * " and to the caveat in proposed § 201.57(f)(10)(ii)(B) that, although no differences between older and younger patient responses had been observed, " * * * greater sensitivity of

some older individuals cannot be ruled out." The comments found these generalizations to be less than helpful and were concerned that they might cause undue caution by health professionals, possibly resulting in suboptimal or even subtherapeutic dosing of elderly patients.

The final rule is intended to provide information to health professionals about a subgroup of the population that may have a different response to certain drug products than the population as a whole. Section 201.57(f)(10)(ii)(A) and (f)(10)(ii)(B) include some words of caution but are phrased carefully to avoid any implication of universal application. FDA does not intend that "Geriatric use" statements substitute for medical judgment, but FDA intends that geriatric labeling information be used, along with professional judgment, as a tool for achieving optimum prescribing practices. The information on prescription drug use in elderly patients required by this final rule will assist health professionals in tailoring drug therapy to the individual needs of patients.

The cautionary tone of § 201.57(f)(10)(ii)(A) and (f)(10)(ii)(B) reflects the agency's opinion that, in general, the greater likelihood of impaired excretory function or impaired homeostatic mechanisms in the elderly does suggest a cautious approach. That caution should not result in a failure to attain therapeutic goals, even if a period of adjustment is necessary to determine the optimum dose for individual patients. If a sponsor believes that particular statements presented in this provision are not appropriate or relevant, the sponsor, under § 201.57(f)(10)(vi), may seek permission to omit these statements or propose an alternative statement.

10. Several comments questioned other specific aspects of the proposed labeling statements and requirements. The comments questioned the terms "sufficient numbers of patients" and "enough elderly patients" as used in proposed § 201.57(f)(10)(ii)(A) and (f)(10)(ii)(B), respectively. The comments asked how many patients would be "sufficient" or "enough" to determine if a particular labeling statement applied. One comment asked if "enough elderly patients" meant enough to reveal differences that are clinically significant or statistically significant.

The question of a sufficient number of subjects arises when analysis shows no difference between younger and older subjects but the small number of subjects available for analysis precludes any real conclusions about the

population as a whole. In such cases, as stated in § 201.57(f)(10)(ii)(A), a labeling statement would, in part, state that clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Adequacy of subject numbers depends on the specific comparisons being made and the number of "events" (therapeutic effects, adverse events) observed, and there is no number that will always constitute "adequate." Thus, smaller numbers could be informative about high-rate events when no difference is found, and a positive finding (a difference) could arise in any size population (and be described under § 201.57(f)(10)(ii)(C)).

FDA advises that, with regard to the phrases "sufficient numbers of subjects aged 65 and over" in § 201.57(f)(10)(ii)(A) and "enough elderly subjects" in § 201.57(f)(10)(ii)(B), participation of at least 100 subjects age 65 and older in clinical studies would allow detection of clinically important differences. This is the number of elderly subjects recommended in the ICH guideline entitled "Studies in Support of Special Populations: Geriatrics." Results in elderly subjects would be compared with those in the (usually) larger number of younger subjects. The information gathered from available sources, as described in § 201.57(f)(10)(ii), would ordinarily be descriptive and not necessarily subject to intense statistical analysis. The primary purpose of examining the information is to detect substantial and consistent (across studies) differences in drug response in the elderly as compared to the overall population. There are problems in interpretation wherever subsets of the overall trial population are examined, but these difficulties do not mean the effort should not be made. Within the limitations of these analyses, however, a finding of "no difference" in a population with less than 100 elderly usually would lead to the statement described in § 201.57(f)(10)(ii)(A), while a finding of no difference in a larger population could lead to the statement in § 201.57(f)(10)(ii)(B). A finding of difference, whatever the population, would lead to labeling as in § 201.57(f)(10)(ii)(C).

FDA's "Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications," which refers to subset analyses, discusses the analysis and presentation of data regarding drug response in different subsets of the population, and the agency's "Guideline for the Study of

Drugs Likely to be Used in the Elderly” specifically relates this discussion to the geriatric population. The ICH guideline “Studies in Support of Special Populations: Geriatrics” reflects sound scientific principles for testing drugs in geriatric populations. FDA recommends consulting these documents for guidance and encourages individuals to contact the agency if questions arise on the sufficiency of data to support “Geriatric use” statements not addressed by the guidelines.

11. One comment said that the use of numbers and percentages required in proposed § 201.57(f)(10)(ii)(B) would be impractical, stating that a burdensome amount of updating and revision would be necessary as new information becomes available. The comment suggested that the statements should address whether “certain thresholds have been reached,” with the agency verifying that the manufacturer has the numbers to support the statements.

The agency disagrees with the comment. The expression of percentages or actual numbers of older subjects involved in clinical studies is an essential part of § 201.57(f)(10)(ii)(B). The percentage or total number of geriatric subjects precedes the statement that “No overall differences in safety or effectiveness were observed between these subjects and younger subjects, * * * but greater sensitivity of some older individuals cannot be ruled out.” This statement applies where sufficient numbers of elderly subjects have taken part in studies to reveal a different response between age groups, but where no differences were detected. The statement suggests that adjusting dosage recommendations for geriatric patients generally will not be necessary. To permit such an implication, it is important to provide practitioners with numbers so that they can weigh the evidence in relation to the needs of an individual patient.

FDA also does not believe that § 201.57(f)(10)(ii)(B) will be overly burdensome or require constant updating. This provision provides for alternative labeling formats using either percentages or the total number of subjects, age 65 and over and age 75 and over, included in clinical studies. The comment may have misunderstood this provision because the percentages refer to the number of subjects included in clinical studies and, unless additional studies are performed, there is no need to update or revise the percentages.

The revised implementation plan should permit ample time for collection and evaluation of data. Manufacturers are urged to contact the agency if they have questions as to the significance of

geriatric data related to this requirement.

12. Several comments addressed proposed § 201.57(f)(10)(iii)(B), which requires a statement in the “Geriatric use” subsection of the labeling for drugs that are substantially excreted by the kidney. The comments asked for more guidance to determine when a drug is “substantially excreted” by the kidney. Another comment suggested that the proposed statement not apply to drugs that are substantially excreted by the kidney but pose no greater risk to patients with renal impairment.

Some drugs, such as phenobarbital, are primarily metabolized and excreted by the liver, while a number of other drugs, such as diuretics, are primarily excreted by the kidneys. The prescriber’s knowledge and experience with the individual patient will determine the course of treatment, and FDA does not feel it would be useful at this time to further quantify this phrase. This provision is intended to alert practitioners to the fact that adequate kidney function is important to the optimum safety and effectiveness of the drug product.

If a sponsor believes that none of the requirements described in paragraphs § 201.57(f)(10)(i) through (f)(10)(v) are appropriate or relevant, the sponsor must provide reasons for the omission of a labeling statement and may propose alternative statements as provided under § 201.57(f)(10)(vi).

13. Another comment recommended that, for drugs that are substantially excreted by the kidney, FDA require pharmacokinetic and pharmacodynamic studies in elderly persons.

As stated earlier in this preamble, although the agency encourages further study of drug effects in the elderly, the rule is not intended to require additional clinical studies. The “Geriatric use” subsection is intended to provide a place in prescription drug labeling where practitioners can find pertinent information that is already available from clinical experience and investigations. For example, in the “Guideline for the Study of Drugs Likely to be Used in the Elderly,” FDA has encouraged assessment of the pharmacokinetic effects of age and of decreased excretory function.

This final rule does not add new requirements for conducting geriatric studies. As stated in the preamble to the regulation on pediatric labeling, various provisions of the Federal Food, Drug, and Cosmetic Act (the act) and the Public Health Service Act (the PHS act), and existing regulations authorize FDA to require such studies under certain circumstances (see section III.C of the

document published in the **Federal Register** of December 13, 1994 (59 FR 64240 at 64242)).

14. A few comments objected to the use of the formula provided in the proposed labeling section for calculating creatinine clearance from a serum creatinine measurement. One comment criticized the specific formula, Cockcroft-Gault (*Nephron* 16:31–41, 1976), pointing out its limitations when applied to older patients, and suggested that another formula, Jelliffe (*Lancet* 1:975–976, 1971), might be more accurate and appropriate for a “Geriatric use” dosage adjustment. Another comment suggested that any formula can become obsolete, and proposed that the regulation not include a formula. The comment said that the agency should instead provide more general guidance for dosing in the presence of kidney impairment that would allow for the use of state-of-the-art assessment tools.

While a survey of available literature indicates that the Cockcroft-Gault formula provides a reasonably good estimate of renal function in the elderly, the agency agrees with concerns that a specific formula might be superseded either by a more precise formula or by a new method for estimating creatinine clearance. Because codification of a specific formula could result in less flexibility and to accommodate possible changes in methods of estimating renal function, FDA has deleted the actual formula from the final rule. The agency, however, wishes to stress the importance of monitoring renal function by calculating creatinine clearance. Creatinine clearance can be measured (often difficult outside the metabolic unit) or can be estimated from a creatinine clearance measurement using a formula.

IV. Implementation

15. Several comments addressed the proposed implementation plan for the “Geriatric use” labeling requirement. Under the proposal, manufacturers would have had 1 year from the date of publication of a final rule to comply with the “Geriatric use” labeling requirements for all products. FDA acknowledged that it may be unable to review all supplements by this effective date, and stated that it would exercise its enforcement discretion not to take action against any product that lacks revised labeling, provided that the applicant has submitted its proposed labeling changes in a timely manner and otherwise acted in good faith to comply with the requirements of the final regulation.

The comments asserted that it would be impossible for companies to comply with the proposed implementation scheme, and that the agency would not have the resources to meet approval dates, thus creating new backlogs in an already over-burdened system. Some comments suggested other timeframes, such as a 2-year, 3-year, or 4-year effective date. Other comments recommended that the agency employ a "staggered implementation scheme," similar to the one used for the implementation of FDA's physician labeling regulations under 21 CFR 201.59.

FDA agrees that the proposed implementation could pose difficulties and has revised the plan to reduce the burdens of compliance on both manufacturers and the agency, while allowing for efficient implementation of the "Geriatric use" labeling requirements. The agency has considered the comments and has adopted a plan that will stagger implementation dates. Because some drug classes and drug products are more likely than others to have a significant impact on geriatric patients, based on existing labeling, research, and reports from health care professionals, FDA has provided for staggered implementation of geriatric labeling requirements to expedite labeling for certain drug products and drug classes. The implementation plan is discussed in greater detail in sections IV.A and B of this document.

Certain changes to an approved application require prior FDA approval of a supplemental application in accordance with § 314.70(b) (21 CFR 314.70(b)) or § 601.12(b). For those products not regulated under section 351 of the PHS act (42 U.S.C. 262), changes to add or strengthen contraindications, warnings, precautions, or adverse reactions or to add or strengthen dosage and administration instructions to increase a product's safety (for products other than biological products) may be put into effect at the time a supplement covering the change is submitted to FDA in accordance with § 314.70(c). Labeling changes should be implemented immediately under § 314.70(c)(2)(i) where additional data or clinical trials indicate a need to add or strengthen a contraindication, warning, precaution, or adverse reaction.

Applicants may make some minor labeling changes to products, other than biological products, without submitting a supplement in accordance with § 314.70(d). The applicant is to describe such changes in the annual report.

Applicants need not obtain prior FDA approval of many supplements. For instance, the statement in the "Geriatric use" subsection can refer to a particular data base. Where the completion of additional clinical trials and accumulation of data simply strengthen conclusions reflected in existing statements in the geriatric labeling, revision of labeling to incorporate these additional numbers may be regarded as changes to strengthen instructions about dosage and administration. Under § 314.70(c)(2)(iii), these labeling changes may be implemented at the time a supplement is submitted to FDA.

For those products regulated under section 351 of the PHS act, labeling changes must be made in accordance with § 601.12. In the **Federal Register** of July 24, 1997 (62 FR 39890), FDA revised the requirements in § 601.12 for the reporting of changes, including the reporting of changes in labeling, to an approved license application. With the revision of § 601.12, manufacturers will be required to implement and report changes in labeling by the same procedures as described above for other drugs.

As noted above, persons who have questions regarding such changes for biological products should contact the appropriate division.

16. One comment argued that manufacturer and agency implementation burdens would be lessened if the geriatric labeling change applied only to those drugs approved in the last 3 to 5 years. The comment claimed that drugs on the market for a longer time (older drugs) have been used to a sufficient extent that practitioners can determine any unique problems encountered by the elderly patient, making a "Geriatric use" subsection unnecessary.

FDA recognizes that while professional experience with older drugs may decrease the need for geriatric labeling, there may be less understanding of the pharmacokinetics of older drugs. Moreover, previously unrecognized problems may be revealed through new research or the circumstances under which drug products are used may change. Such a situation could, for example, result from the discovery of an adverse interaction in geriatric patients between an older drug product and one that has recently been approved.

FDA further recognizes that ease of compliance with this final rule may vary depending on the amount of, and the ability to access, available information. The implementation plan for this final rule takes these and other factors into account to minimize

burdens for manufacturers. For instance, the agency expects that the need for a "Geriatric use" subsection often may be greatest for recently approved drugs where there is little collective professional experience with the drug in older patients. In addition, this information is most likely to be readily available to manufacturers from a current data base. Likewise, the agency expects geriatric use information for drugs that have been marketed for a longer period of time will be more extensive and more diffuse, and thus more difficult to retrieve and summarize. Printed reports and clinical data for these drugs may be scattered and less likely to have been processed and stored in a computer data base than would be the case for more recently approved drugs. In these cases, a manual search to gather available information may be necessary. The implementation plan for this final rule recognizes that the necessity for such a search is likely to be directly related to the date of an NME approval or biological product license approval. Therefore, under the implementation scheme for the final rule, sponsors will be required to submit geriatric labeling supplements at an earlier date for more recently approved products than for products that have been marketed for a longer time. The agency believes that this implementation plan will allow manufacturers to work within a reasonable timetable to craft meaningful and usable "Geriatric use" labeling.

As discussed in section IV, comment 15 of this document, the implementation plan has been revised to reduce the burdens of compliance for both the agency and manufacturers. In revising the implementation plan, the agency specifically considered and addressed the concerns associated with drugs that have been marketed for a number of years. The revised plan gives manufacturers of these drugs longer periods of time to submit geriatric labeling. At the same time, the agency has determined that priority should be given to implementation for certain categories of drugs that either alone or in combination with other drug products may be more likely to cause problems in geriatric patients.

Implementation of the "Geriatric use" subsection of prescription drug labeling is as follows:

A. Priority Implementation

Geriatric patients are more likely to have more problems with certain classes of drugs than with others because of the following: Age-induced physiological changes in the patient, the narrow therapeutic range of some drug

products, and the potential for drug-drug and drug-disease interactions, as well as other factors. The revised labeling for drugs subject to priority implementation must be submitted to FDA by August 27, 1998. FDA has therefore selected the following drug classes or drug products for priority implementation:

1. Psychotropic Drugs:

- a. Antidepressants,
- b. Anxiolytics,
- c. Hypnotics, and
- d. Antipsychotics;

2. Nonsteroidal Anti-inflammatory Drugs (NSAID's);

3. Digoxin, Antiarrhythmics, and Calcium Channel Blockers;

4. Oral Hypoglycemics;

5. Anticoagulants; and

6. Quinolones.

B. Implementation Based on the NME or Biological Product License Approval Date

All drug products not subject to priority implementation, must comply with this regulation on the basis of the year in which the drug product's NME (active moiety) or biological product license was first approved. For combination products, application holders must determine the approval date of the earliest NME or biological product license. That earlier date will be the controlling date for implementation purposes. The date of issuance of a biological product license should be used for a combination biological product.

FDA is aware that, for a variety of reasons, drug products subject to approved drug applications are not always marketed. An approved product may, for example, be withheld from the marketplace for economic reasons. Later, when conditions change, the drug may be manufactured and actively marketed. To further lessen the burden of implementing this rule, FDA will not require geriatric labeling for approved products that are not currently marketed, including products selected for priority implementation. If, however, an unmarketed approved drug product is subsequently marketed, the product must include appropriate geriatric labeling at the time it is marketed.

The implementation schedule is based on the NME or biological product license approval date as follows:

1989 to present: Revised labeling due August 27, 1999,

1982 through 1988: Revised labeling due August 28, 2000,

1975 through 1981: Revised labeling due August 27, 2001,

1963 through 1974: Revised labeling due August 27, 2002, and

Prior to 1963: Revised labeling due August 27, 2003.

FDA will notify all holders of approved abbreviated applications of the changes in the listed product's geriatric labeling and provide directions on how to incorporate the new text in the labeling. All holders of approved abbreviated applications for which there is no reference listed new drug application (NDA) drug product in the prescription drug product list section of the publication entitled *Approved Drug Products with Therapeutic Equivalence Evaluations* are expected to comply with the implementation plan described in sections IV.A and B of this document by submitting geriatric labeling.

The agency encourages sponsors to voluntarily implement these provisions prior to the scheduled implementation date, where feasible.

All supplements submitted under this rule should be noted as "Geriatric Labeling Supplement" in the "Reason for Submission" block.

V. Legal Authority

This final rule to revise prescription drug labeling regulations to require a "Geriatric use" subsection is authorized by the act and by the PHS act. Section 502(a) of the act (21 U.S.C. 352(a)) prohibits false or misleading labeling of drugs, including, under section 201(n) of the act, failure to reveal material facts relating to potential consequences under customary conditions of use. Section 502(f) of the act identifies as misbranded any drug whose labeling does not bear adequate directions for use, as well as such adequate warnings against unsafe dosage or methods or duration of administration as are necessary to protect users. In addition, section 502(j) defines as misbranded those drugs that are dangerous to health when used in the manner prescribed, recommended, or suggested in their labeling.

In addition to the misbranding provisions, the premarketing approval provisions of the act authorize FDA to require that prescription drug labeling provide the practitioner with adequate information to permit the safe and effective use of the drug product. Under section 505 of the act (21 U.S.C. 355), FDA will approve an NDA only if the drug is shown to be both safe and effective for its intended use under the conditions set forth in the drug's labeling. Section 701(a) (21 U.S.C. 371(a)) authorizes FDA to issue

regulations for the efficient enforcement of the act.

Under § 201.100(d) of FDA's labeling regulations, prescription drug products must bear labeling that contains adequate information under which licensed practitioners can use the drug safely for its intended purposes. Section 201.57 describes specific categories of information, including information for drug use in selected subgroups of the general population, which must be present to meet the requirements of § 201.100. In addition, under § 314.125 (21 CFR 314.125), FDA will not approve an NDA unless, among other things, there is adequate safety and effectiveness information for the labeled indications.

Section 351 of the PHS act provides legal authority for the agency to regulate biological products, including labeling. Licenses for biological products are to be issued only upon a showing that they meet standards "designed to insure the continued safety, purity, and potency of such products" prescribed in regulations (42 U.S.C. 262(d)). The "potency" of a biological product includes its effectiveness (21 CFR 600.3(s)). Section 351(b) of the PHS act prohibits falsely labeling a biological product. FDA's regulations at 21 CFR part 201 apply to all prescription drug products, including biological products.

A drug product not in compliance with § 201.57(f)(10) of this final rule would be considered to be misbranded and an unapproved new drug under the act. A noncomplying product that is a biological product would, in addition, be considered falsely labeled and an unlicensed biological under the PHS act.

VI. Analysis of Impacts

A. Introduction

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). If a rule has a significant impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize the impact of that rule on small entities. The agency believes that this final rule is consistent with the regulatory philosophy and principles

identified in Executive Order 12866 and the Regulatory Flexibility Act.

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). The 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 following discussion presents FDA's assessment of the direct costs that the rule will impose on the prescription drug industry. (Further background data are provided in the agency report entitled "Threshold Assessment of Requirements for Geriatric Labeling" on file at the Dockets Management Branch (Ref 3).)

Comments to the agency by an innovator trade group and one large innovator firm (a pharmaceutical firm that develops new drugs) indicated that the proposed requirements would impose a severe economic burden. However, these comments provided no written estimates of either the expected costs or the extent of the research effort that would be needed to comply with the new provisions. FDA's cost estimates, therefore, are based on extrapolations from various agency data bases and plausible assumptions of unit costs. The estimates took into account the number of labels affected, the estimated availability of data on the elderly, the estimated availability of computerized data files, and the amount of existing geriatric labeling. Costs that

are not considered include possible industry efforts to conduct new clinical trials to generate data on problems unique to the elderly, possible market shifts among competing products due to changes in labeling, possible displacement of industry workers due to the costs of the regulatory requirements, or any other costs beyond direct effects. Because part of this analysis was prepared in 1993, in support of this final rule as then drafted, much of the underlying data are several years old. As explained below, the use of more recent data would probably project significantly lower costs.

B. Methodology

Estimating the costs to industry required several steps. Data on numbers of marketed drugs, use by the elderly, the frequency of labeling supplement approvals, and the existence of geriatric labeling were available from FDA data files or from previously conducted studies. Information on the effort required to determine appropriate label changes and physically change labels was developed from industry sources and drug reviewing officials within FDA.

1. Number and Age of Products Affected

Two separate analyses were conducted to estimate the number of products affected by the rule. One analysis estimated the number of innovator products, and the other, the number of generic products that would be subject to the rule. An analysis of 1993 IMS America data on marketed products (data derived from a proprietary data base in the National Disease and Therapeutic Index maintained by IMS America; Plymouth Meeting, PA) determined that about 1,578 innovator labels would be subject

to the rule. The actual number of innovator product labels subject to the rule is probably slightly larger than this number because the IMS data collection methodology most likely missed very small volume products. However, because there is no easy way to estimate the number of omitted products and the degree of error is thought to be of little practical significance, the counted number of products was used.

Conversations with industry representatives indicated that the process of complying with the regulation would be much more difficult for drugs that have been marketed for a longer time. Products approved before 1975, and in some cases before 1980, lack computer readable clinical trial data. Therefore, subgroup analysis of these early data would require some data entry directly from data recording sheets or individual patient records. Most clinical trial data used for products approved since 1985 are already in an easily analyzable form. However, some data for products approved between 1975 and 1985, although computerized, would not be in a compatible format. This data would require additional manipulation before subgroup analysis could be performed.

Table 1 shows the distribution of the 1,578 innovator products by year of FDA approval. Based on the trend of automation described previously, geriatric labeling compliance will become progressively less expensive with the more recent the date of drug product approval. Compliance activities for products approved after 1985 will cost less than for products approved between 1975 and 1984. Products approved before 1975 will require the greatest expenditure.

TABLE 1—NUMBER OF INNOVATOR PRODUCTS BY YEAR OF FDA APPROVAL

Year	Approvals
Pre-1975	1,191
1975 to 1984	199
1985 to 1991	188
Total	1,578

An analysis of abbreviated new drug application (ANDA) approvals conducted in July 1996, found 2,417 generic products (excluding different strengths and package sizes) approved for marketing at that time. The estimated costs for labeling changes in section VI.C of this document are based on all 2,417 generic products. Although not insignificant, these costs will be considerably less than the costs for innovator products.

2. Current Incidence of Geriatric Use

Ideally, the agency would like to have had access to data on geriatric subjects included in clinical trials for all approved drugs currently marketed. Such information would have helped determine the cost and effort required to analyze the data and the likelihood that the data would prove useful for labeling revisions. Although the elderly are the largest consumers of certain drug products (e.g., for the treatment of

cancer and cardiovascular disease), in the past elderly individuals were not commonly included in controlled clinical trials. Therefore, clinical data on elderly patients for drugs that have been marketed for many years will be sparse—even for drugs commonly used by the elderly. Recently, elderly individuals have been included and identified as a subgroup in clinical trials. Consequently, more data will be

available for recently approved products.

Because comprehensive summary data on geriatric subjects in clinical trials do not currently exist, insight on the incidence of geriatric use was gained for this analysis from IMS America data on the number of times a product was mentioned during a doctor/patient visit or phone conversation. Specifically, annual statistics were generated (as of the year ending September 30, 1991) on the number of product mentions for all patients and for patients age 65 and older for all prescription products. The term "mention" means that a specific drug was recommended, prescribed, or handed to the patient by the physician. Although the actual number of instances where the patient used the product may be different than the number of mentions, this analysis used only the ratio of elderly use to total use, which tended to cancel out any significant bias.

The raw data on product mentions were summarized into therapeutically equivalent product groups to account for the 1,578 innovator products marketed in 1991. Geriatric use ranged from nearly zero to almost 100 percent depending on the product. The analysis showed that fully half of the innovator products are infrequently used by the elderly—that is, geriatric patients constitute less than 25 percent of the market share for 789 of the 1,578 products. By contrast, the elderly constitute more than 50 percent of the market share for a quarter of the innovator products. This information does not indicate the percentage of elderly subjects participating in clinical trials. In recent years, however, geriatric participation in clinical trials for drug products frequently used by the elderly has increased, and it is likely that less frequent use of a drug product by geriatric patients is consistent with low

participation by the elderly in clinical trials for that product.

3. Current Incidence of Geriatric Labeling

In 1989, FDA's Division of Drug Advertising and Labeling conducted a survey of geriatric labeling covering the top 25 drug products used by the elderly and all products in the top 12 classes of drugs used by the elderly. This survey included 425 products including 370 innovator products and 55 generic products. Because the labeling survey did not provide geriatric labeling information for all products, and the geriatric labeling that was found on the surveyed labels did not typically comply fully with the regulation, FDA has used the survey results in this analysis as an indicator of potential data availability, rather than an indicator of compliance with the regulation.

A detailed comparison of the incidence of the geriatric labeling data with the geriatric use data showed that products falling in the middle range of geriatric use have a higher incidence of geriatric labeling than those products with relatively low and relatively high geriatric use. (See FDA's "Threshold Assessment of Requirements for Geriatric Labeling" for a graphical illustration of these respective distributions (Ref. 3).) This finding was unexpected. Particularly curious was the low incidence of geriatric labeling among the high geriatric use products. One possible explanation is that a high degree of geriatric use was assumed, but discussions with industry representatives could not confirm this hypothesis.

4. Products By Cost Category

As noted in section VI.B.2 of this document, the geriatric use of 75 percent of the products surveyed is less than 50 percent. FDA assumed that the availability of geriatric data (at least some analyzable data) would not exceed the incidence of geriatric labeling found

in the previously described labeling survey. For the 25 percent of the surveyed products for which geriatric use constituted more than 50 percent of total use (high use), the agency assumed that analyzable data exists for the proportion of products that currently have geriatric labeling and that at least some data exist for the remaining products. These distributions led to the construction of four distinct groups of products based on the degree of geriatric use and the availability of geriatric data, roughly defined as follows:

- (1) Low geriatric use products with no data available (no incidence of geriatric labeling)—about half of the low elderly use products.
- (2) Low geriatric use products with some data available (at least some geriatric labeling)—about half of the low elderly use products.
- (3) High geriatric use products with limited data available (no incidence of geriatric labeling)—about half of the high elderly use products.
- (4) High geriatric use products with data available (at least some geriatric labeling)—about half of the high elderly use products.

These four product label groups, combined with the distribution of new drug approvals shown in Table 1, provide the basis for FDA's estimated costs. Table 2 displays the estimated number of product labels falling into each of 16 cost categories. The two low geriatric use categories account for three-quarters (three-eighths each) of the products in each column and the high use categories account for one-fourth (one-eighth each) of the products. The two columns under the 1975 to 1984 heading account for the differences in the way the data are likely to be stored—half in a form readable by the computer technology used today and half in a form that will require some effort to reformat.

TABLE 2—INNOVATOR PRODUCTS PER COST CATEGORY

Geriatric Use and Data Availability	Pre-1975	1975 to 1984		1985 to 1991	Totals
		Formatted Data	Unformatted Data		
Low Use/ No Data	447	38	37	71	592
Low Use/ Some Data	447	38	37	71	592
High Use/ Limited Data	149	13	12	24	197
High Use/ Some Data	149	13	12	24	197
Totals ¹	1,191	100	99	188	1,578

¹ Column totals may not add due to rounding

Table 3 provides estimates of the average cost per product of complying with the regulation for each geriatric use/geriatric data category shown in Table 2. These values were arrived at

after discussing anticipated industry effort to comply with the regulation with several industry officials, and after considering FDA's own experience conducting short-term studies requiring

data retrieval, data formatting, and data analysis. The category costs, therefore, are based on subjective, but reasonable, estimates of the levels of effort likely to be involved.

The highest costs (\$24,000) are for drug products approved before 1975 for which extensive geriatric data exist, but such data are not available in a computer readable format. In this case, at a minimum, the data would have to be extracted from subject records, entered into a computer file, and analyzed. The results would be compared with summary data on all remaining subjects included in the

clinical trials to detect any significant geriatric differences.

Calculations assume that this process, including a literature search and label and supplement preparation, would take about three person-months (the amount of time a person works in 3 months) at a loaded cost of about \$50 per person-hour. The least complicated case (\$4,000), would be for drug products with no data available on

geriatric patients. A literature search would have to be conducted, the label revised, and a supplement submitted to reflect the revision. This process was estimated to take about two person-weeks at the same hourly rate. The remaining cost categories fall between the two just described with differing levels of effort requiring differing levels of costs.

TABLE 3—INNOVATOR COSTS PER PRODUCT BY PRODUCT CATEGORY

Geriatric Use and Data Availability	Pre-1975	1975 to 1984		1985 to 1991
		Formatted Data	Unformatted Data	
Low Use/ No Data	\$4,000	\$4,000	\$4,000	\$4,000
Low Use/ Some Data	\$8,000	\$6,000	\$8,000	\$6,000
High Use/ Limited Data	\$16,000	\$6,000	\$8,000	\$6,000
High Use/ Some Data	\$24,000	\$6,000	\$8,000	\$6,000

C. Total Costs of Compliance

The category costs in Table 3 were multiplied by the numbers of labels shown in Table 2 and summed over all

categories to arrive at the estimated total costs of compliance for the innovator products. These results are shown in Table 4. Clearly, the greatest costs of the regulation will be for products approved

before 1975. These products account for \$11,314,500, or 84 percent of the total \$13,470,000 estimated costs for innovators, as shown in Table 4.

TABLE 4—TOTAL INNOVATOR COMPLIANCE COSTS BY CATEGORY

Geriatric Use and Data Availability	Pre-1975	1975 to 1984		1985 to 1991	Totals
		Formatted Data	Unformatted Data		
Low Use/ No Data	\$1,786,500	\$150,000	\$148,500	\$282,000	\$2,367,000
Low Use/ Some Data	\$3,573,000	\$225,000	\$297,000	\$423,000	\$4,518,000
High Use/ Limited Data	\$2,382,000	\$75,000	\$99,000	\$141,000	\$2,697,000
High Use/ Some Data	\$3,573,000	\$75,000	\$99,000	\$141,000	\$3,888,000
Totals	\$11,314,500	\$525,000	\$643,500	\$987,000	\$13,470,000

FDA's estimates the cost of relabeling each generic product to be \$2,000, which accounts for the supplement preparation, the revision and printing of labels based on changes made to innovator product labels, and the destruction of small stocks of existing labels. Thus, the total estimated cost of relabeling 2,417 generic products is \$4,834,000, bringing the total estimated cost of the regulation to \$18,304,000. Manufacturers of innovator products will incur about 74 percent and manufacturers of generic products about 26 percent of this total.

Although these projections are the best available to the agency, FDA notes that there are reasons to believe that they overstate the likely consequences of the rule. For example:

(1) Part of the analysis is based on data that are several years old, and a greater percentage of products now on the market are thought to be close to compliance with the final rule. Many recently approved NME's (those approved since 1991) contain a geriatric

labeling section and already comply with the rule. Moreover, several of the older drug products that would not comply with the rule have been removed from the market since 1991.

(2) The rule applies only to approved products that are actually marketed. This cost analysis, however, assumes that all approved NME's would be subject to the provisions of the rule. Adjusting for these differences would substantially reduce the estimated costs to industry.

D. Effects on Small Entities

The affected pharmaceutical companies can be classified into three industry sectors: Large innovator firms (more than 750 employees), small innovator firms (fewer than 750 employees), and independent generic firms (fewer than 750 employees). Within the two innovator sectors, almost all of the costs will be borne by the large innovators because large firms sponsor almost all innovator product applications. Although the occasional

product sponsored by a small innovator firm may require additional research and analysis to support geriatric labeling, it is unlikely that any one small firm would have more than one or two such products or that any one of these products would be marketed if it could not generate over several hundred thousand dollars of revenue per year. As firms have up to 6 years to comply with the rule for all products, the estimated one-time cost per product of \$6,000 to \$24,000 would be extremely low relative to the income generated from such product(s) during this period.

Most of the small firms affected by the rule will be independent manufacturers of generic drugs. These firms will incur the cost of changing the labels of numerous drug products. The following example illustrates that even the largest of these small firms would not likely incur significant costs in comparison to company revenues. For example, one of the largest independent generic manufacturers (350 employees) held ANDA's in 1995 for approximately 250

products containing 95 chemical entities. According to their 10-k filing with the Securities and Exchange Commission, the company marketed only 37 drug products containing 21 chemical entities in mid-1995. Therefore, the firm would need to make about 21 label changes at a total cost of about \$42,000. Not all of these costs would be incurred during the same year, however, because the regulation will be phased in over a 6-year period. Considering these circumstances, the \$42,000 cost to this small entity would not be a significant fraction of the company's \$200 million in annual sales.

Although the previous example applies to just one firm, given the estimated \$2,000 compliance cost for each marketed generic drug, it is difficult to construct a scenario in which the cost of the required label changes could constitute a significant portion of a company's 6-year revenue stream. As a result, although most manufacturers of generic drugs will be affected, very few, if any, will incur costs that are significant in comparison with company revenues. FDA therefore certifies that this rule will not have a significant effect on a substantial number of small entities.

VII. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(11) 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 final rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The following title, description, and respondent description of the information collection provisions are shown with an estimate of the annual reporting burden. This estimate includes the time needed for reviewing instructions, gathering and maintaining

the data needed, and completing and reviewing the collection of information.

Most of the paperwork burden imposed by this final rule will be a one-time reporting burden associated with gathering data and designing and manufacturing new labeling that includes a geriatric use subsection in the "Precautions" section of the labeling. The paperwork burden will vary widely, with the most significant burden, up to 480 hours, estimated for some innovator drug products approved before 1975. By contrast, the burden for most generic drug products is estimated at 80 hours or less.

In response to comments and on its own initiative, FDA has made a number of changes in the final rule to ease the paperwork burden. First, for the great majority of products affected by this regulation, the revised implementation dates will permit manufacturers sufficient time to design and print new labeling and deplete existing stocks of old labeling before the geriatric subsection is required for the product. Second, FDA will not require geriatric labeling to be submitted for approved products that are not currently marketed. Third, all of the labeling language under § 201.57(f)(10)(ii)(A), and much of the labeling language under § 201.57(f)(10)(ii)(B) and (f)(10)(ii)(C) are provided in the regulation. Fourth, as discussed in section IV of this document, many NME's approved since 1991 contain a geriatric labeling section and are already in compliance, and the labeling of a substantial number of drug products approved before 1991 contains some geriatric information.

Title: Geriatric Use Labeling for Human Prescription Drugs.

Description: FDA is amending its regulations governing the content and format of labeling for human prescription drug products, including biological products, to include information on the appropriate use of drugs for persons 65 and older.

Description of Respondents: Business and other for-profit organizations, including small businesses and manufacturers.

Because labeling was not considered collection of information under the Paperwork Reduction Act of 1980, the agency did not provide a paperwork comment period for the proposed rule. However, the agency is providing an opportunity for public comment under the Paperwork Reduction Act of 1995, which was enacted 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 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 October 27, 1997. 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 5—ESTIMATED ANNUAL REPORTING BURDEN

21 CFR Section	Annual no. of respondents	Hours per response	Total burden hours
201.57(f)(10)	290	120	34,800

IX. References

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. Rochon, P. A., and J. H. Gurwitz, "Drug Therapy," *Lancet* 346(8966):32-36, 1995.

2. Schneider, J. K., L. C. Mion, and J. D. Frengley, "Adverse Drug Reactions in an Elderly Outpatient Population," *American Journal of Hospital Pharmacy*, 49(1):90-96, 1992.

3. Food and Drug Administration, "Threshold Assessment of Requirements for Geriatric Labeling," June 30, 1997.

List of Subjects in 21 CFR Part 201

Drugs, Labeling, 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 part 201 is amended as follows:

PART 201—LABELING

1. The authority citation for 21 CFR part 201 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 508, 510, 512, 530–542, 701, 704, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 358, 360, 360b, 360gg–360ss, 371, 374, 379e); secs. 215, 301, 351, 361 of the Public Health Service Act (42 U.S.C. 216, 241, 262, 264).

2. Section 201.57 is amended by adding new paragraph (f)(10) to read as follows:

§ 201.57 Specific requirements on content and format of labeling for human prescription drugs.

* * * * *

(f) * * *

(10) *Geriatric use.* (i) A specific geriatric indication, if any, that is supported by adequate and well-controlled studies in the geriatric population shall be described under the "Indications and Usage" section of the labeling, and appropriate geriatric dosage shall be stated under the "Dosage and Administration" section of the labeling. The "Geriatric use" subsection shall cite any limitations on the geriatric indication, need for specific monitoring, specific hazards associated with the geriatric indication, and other information related to the safe and effective use of the drug in the geriatric population. Unless otherwise noted, information contained in the "Geriatric use" subsection of the labeling shall pertain to use of the drug in persons 65 years of age and older. Data summarized in this subsection of the labeling shall be discussed in more detail, if appropriate, under "Clinical Pharmacology" or the "Clinical Studies" section. As appropriate, this information shall also be contained in "Contraindications," "Warnings," and elsewhere in "Precautions."

(ii) Specific statements on geriatric use of the drug for an indication approved for adults generally, as distinguished from a specific geriatric indication, shall be contained in the "Geriatric use" subsection and shall

reflect all information available to the sponsor that is relevant to the appropriate use of the drug in elderly patients. This information includes detailed results from controlled studies that are available to the sponsor and pertinent information from well-documented studies obtained from a literature search. Controlled studies include those that are part of the marketing application and other relevant studies available to the sponsor that have not been previously submitted in the investigational new drug application, new drug application, biological license application, or a supplement or amendment to one of these applications (e.g., postmarketing studies or adverse drug reaction reports). The "Geriatric use" subsection shall contain the following statement(s) or reasonable alternative, as applicable, taking into account available information:

(A) If clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether elderly subjects respond differently from younger subjects, and other reported clinical experience has not identified such differences, the "Geriatric use" subsection shall include the following statement:

"Clinical studies of (name of drug) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy."

(B) If clinical studies (including studies that are part of marketing applications and other relevant studies available to the sponsor that have not been submitted in the sponsor's applications) included enough elderly subjects to make it likely that differences in safety or effectiveness between elderly and younger subjects would have been detected, but no such differences (in safety or effectiveness) were observed, and other reported clinical experience has not identified such differences, the "Geriatric use" subsection shall contain the following statement:

Of the total number of subjects in clinical studies of (name of drug), — percent were 65 and over, while — percent were 75 and over. (Alternatively, the labeling may state the total number of subjects included in the studies who were 65 and over and 75 and over.) No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical

experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

(C) If evidence from clinical studies and other reported clinical experience available to the sponsor indicates that use of the drug in elderly patients is associated with differences in safety or effectiveness, or requires specific monitoring or dosage adjustment, the "Geriatric use" subsection of the labeling shall contain a brief description of observed differences or specific monitoring or dosage requirements and, as appropriate, shall refer to more detailed discussions in the "Contraindications," "Warnings," "Dosage and Administration," or other sections of the labeling.

(iii)(A) If specific pharmacokinetic or pharmacodynamic studies have been carried out in the elderly, they shall be described briefly in the "Geriatric use" subsection of the labeling and in detail under the "Clinical Pharmacology" section. The "Clinical Pharmacology" section and "Drug interactions" subsection of the "Precautions" section ordinarily contain information on drug-disease and drug-drug interactions that is particularly relevant to the elderly, who are more likely to have concomitant illness and to utilize concomitant drugs.

(B) If a drug is known to be substantially excreted by the kidney, the "Geriatric use" subsection shall include the statement:

"This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function."

(iv) If use of the drug in the elderly appears to cause a specific hazard, the hazard shall be described in the "Geriatric use" subsection of the labeling, or, if appropriate, the hazard shall be stated in the "Contraindications," "Warnings," or "Precautions" section of the labeling, and the "Geriatric use" subsection shall refer to those sections.

(v) Labeling under paragraphs (f)(10)(i) through (f)(10)(iii) of this section may include statements, if they would be useful in enhancing safe use of the drug, that reflect good clinical practice or past experience in a particular situation, e.g., for a sedating drug, it could be stated that:

"Sedating drugs may cause confusion and over-sedation in the elderly; elderly patients generally should be started on low doses of (name of drug) and observed closely."

(vi) If the sponsor believes that none of the requirements described in

paragraphs (f)(10)(i) through (f)(10)(v) of this section is appropriate or relevant to the labeling of a particular drug, the sponsor shall provide reasons for omission of the statements and may propose an alternative statement. FDA may permit omission of the statements if FDA determines that no statement described in those paragraphs is appropriate or relevant to the drug's labeling. FDA may permit use of an alternative statement if the agency determines that such statement is accurate and appropriate.

* * * * *

Dated: July 31, 1997.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 97-22701 Filed 8-26-97; 8:45 am]

BILLING CODE 4160-01-F

DEPARTMENT OF TRANSPORTATION

Federal Highway Administration

23 CFR Parts 140 and 646

[FHWA Docket No. FHWA-97-2681]

RIN 2125-AD86

Railroad/Highway Projects

AGENCY: Federal Highway Administration (FHWA), DOT.

ACTION: Interim final rule; request for comments.

SUMMARY: The FHWA is amending its regulations on railroad/highway projects and reimbursement for railroad work on Federal-aid highway projects. The amendments require railroads to: Submit final billings within one year following completion of the railroad work; remove the requirement of a State's certification that work is complete; remove the "G" Funds terminology; increase the ceiling for lump sum agreements from \$25,000 to \$100,000; incorporate changes brought about by the Intermodal Surface Transportation Efficiency Act of 1991 (ISTEA), Public Law 102-240, 105 Stat. 1914; and show dimensions for participation limits in metric units. The FHWA makes these changes to conform the existing railroad/highway regulations to more recent laws or regulations, and to provide State highway agencies with clarification and more flexibility in implementing the current law. This rulemaking is part of the FHWA's effort to implement the President's Regulatory Reinvention Initiative.

DATES: This interim final rule is effective August 27, 1997. Written

comments must be submitted on or before October 27, 1997.

ADDRESSES: Submit written, signed comments to the docket number that appears in the heading of this document to the Docket Clerk, U.S. DOT Dockets, Room PL-401, 400 Seventh Street, SW., Washington, D.C. 20590-0001. All comments received will be available for examination at the above address between 10 a.m. and 5 p.m., e.t., Monday through Friday, except Federal holidays. Those desiring notification of receipt of comments must include a self-addressed, stamped envelope or postcard.

FOR FURTHER INFORMATION CONTACT: Robert Winans, Office of Engineering, (202) 366-0450, or Wilbert Baccus, Office of the Chief Counsel, (202) 366-0780, FHWA, 400 Seventh Street, SW., Washington, D.C. 20590. Office hours are from 7:45 a.m. to 4:15 p.m., e.t., Monday through Friday, except Federal holidays.

SUPPLEMENTARY INFORMATION: Present FHWA regulations regarding railroad/highway projects and reimbursement for railroad work on Federal-aid highway projects have evolved from basic principles established decades ago, with many of the policies remaining unchanged. The present regulations are found at 23 CFR part 140, subpart I, and part 646, subpart B. The FHWA amends these regulations in the following manner and for the reasons set forth below.

In part 140, subpart I, § 140.904, paragraph (b)(1) is amended to clarify that the approved program of projects is the approved statewide transportation improvement program, as is now required under 23 U.S.C. 135.

In § 140.922, paragraph (b) is amended to require railroads to submit final billings within one year following completion of the railroad work. Otherwise, previous payments to railroads may be considered final and projects may be closed out. This change will assist highway agencies in their efforts to obtain timely final billings from the railroads. Prior to this action, it had been common for some railroad bills to be received years after the work was completed, thus delaying audit activity and project closure. With the amended language, billings received from railroads after one year following completion of the railroad work can be paid at the discretion of the highway agency. Paragraph (b) is further amended to remove the requirement for State certification that the work is complete, acceptable, and in accordance with the terms of the agreement. The FHWA believes that such certificates are

not necessary on individual projects. Instead, compliance can be reviewed on a program basis.

In part 646, subpart B, § 646.200, paragraph (c) is amended to refer to current sections of highway law. Section 405 of title 23, U.S.C., was repealed and section 203 of the Highway Safety Act of 1973 (Pub. L. 93-87, 87 Stat. 282) was codified as part of 23 U.S.C. 130. Paragraph (f) is removed because part 170 of title 23, CFR, no longer exists.

Section 646.202, Authority, is removed and reserved. This section is removed because the authority citation is placed at the part level and, therefore, redundant as a separate section in subpart B.

Section 646.204 is amended to remove paragraph (d) which defines obsolete terminology, to remove the paragraph designations from all definitions, and to place the definitions in alphabetical order.

In § 646.208, paragraphs (a) and (b) are revised to describe only funding sources for rail/highway crossing projects. Information contained in this section on Federal share is moved to § 646.212.

The current text of § 646.212, paragraph (b) is removed. Section 1012(a) of the ISTEA amended 23 U.S.C. 120 by removing subsection (d) concerning Federal share payable for reconstruction of existing grade separation projects on railway/highway crossings. Such projects are no longer eligible for 100 percent Federal funding. Regulatory text from § 646.208(b) is redesignated and revised as a new paragraph (b) in § 646.212 in order to provide information on Federal share in one place.

In § 646.214, paragraph (a)(2) is amended to clarify that the FHWA no longer is required to approve standards for all Federal-aid projects. Section 1016(d) of the ISTEA amended 23 U.S.C. 109 by adding a new subsection (p) which provided that non-NHS projects now follow State approved standards.

In § 646.216, paragraph (d)(3)(ii) is amended to increase the ceiling from \$25,000 to \$100,000 for using the lump sum payment arrangement for reimbursement for railroad adjustments (other than installation or improvement of grade crossing warning devices and/or grade crossing surfaces) on Federal-aid and direct Federal highway projects. The amendment provides the States greater flexibility in utilizing the lump sum payment arrangement. The purpose of allowing lump sum agreements, in lieu of agreements based on an accounting of actual costs, is to reduce the administrative burden associated