
Guidance for Industry

Content and Format for Geriatric Labeling

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

**October 2001
Labeling**

Guidance for Industry

Content and Format for Geriatric Labeling

Additional copies of this Guidance are available from:

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

or

*Office of Communication, Training and
Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
<http://www.fda.gov/cber/guidelines.htm>.
Fax: 1-888-CBERFAX or 301-827-3844
Phonel: the Voice Information System at 800-835-4709 or 301-827-1800.*

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

**October 2001
Labeling**

TABLE OF CONTENTS

I. INTRODUCTION..... 1

II. BACKGROUND..... 1

**III. APPLICATION HOLDERS' RESPONSIBILITY FOR SUBMITTING
REVISED LABELING..... 2**

IV. IMPLEMENTATION OF THE GERIATRIC LABELING RULE..... 3

V. DESCRIPTION OF REGULATION AND OPTIONAL STANDARD LANGUAGE..... 5

VI. CONTENT AND FORMAT..... 7

A. Cover Letter..... 7

B. Detailed Table of Contents..... 7

C. Revised Labeling..... 7

D. Applicable Regulatory Paragraph(s)..... 8

E. User Fee..... 8

F. Data to Support Geriatric Use Labeling..... 8

**VII. APPLICABILITY OF USER FEES TO GERIATRIC LABELING
SUPPLEMENTS..... 10**

VIII. QUESTIONS REGARDING 21 CFR 201.57(f)(10)..... 10

GUIDANCE FOR INDUSTRY¹

Content and Format for Geriatric Labeling

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION

In a final rule published in the *Federal Register* on August 27, 1997 (62 FR 45313), FDA established the *Geriatric Use* subsection in the labeling for human prescription drug and biological products to provide pertinent information about the use of those products in the elderly.

This guidance is intended to provide industry with information on submitting geriatric labeling of human prescription drug and biological products. This guidance discusses the following issues related to the submission of geriatric labeling:

- Who should submit revised labeling
- Implementation dates
- Description of the regulation and optional standard language in proposed labeling
- Content and format for geriatric labeling
- Applicability of user fees to geriatric labeling supplements

II. BACKGROUND

In 1997, FDA established the *Geriatric Use* subsection, as a part of the PRECAUTIONS section, in the labeling for human prescription drugs to include more complete information about the use of a drug or biological product in the elderly (persons aged 65 years and over) (21 CFR 201.57 (f)(10)). As a result, many application holders are required to submit geriatric labeling supplements under 21 CFR 314.70 or 601.12. These supplements require Agency approval prior to implementation except (1) in cases where the labeling change adds or strengthens a precaution

¹ This guidance has been prepared by the Geriatric Subcommittee of the Medical Policy Coordinating Committee (MPCC), Center for Drug Evaluation and Research (CDER), and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

or dosage and administration instruction as outlined in ' 314.70(c)(2) or § 601.12(f)(2)² and (2) for labeling changes submitted 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).³

III. APPLICATION HOLDERS' RESPONSIBILITY FOR SUBMITTING REVISED LABELING

Under the geriatric labeling regulation, drug products fall into one of three categories with regard to submission of geriatric labeling supplements (Table 1). For drug products in the first category, which includes all marketed drug products with an approved new drug application (NDA) or biologics license application (BLA) and products marketed under an approved abbreviated new drug application (ANDA) where the ANDA product is the reference listed drug,⁴ the submission is to include revised labeling and the data supporting the revision. For drug products in the second category, which includes marketed drug products for which there is no approved application, unmarketed drugs with an approved NDA, BLA, or ANDA, and over-the-counter (OTC) drug products,⁵ no submission is necessary. For drug products in the third category (i.e., marketed products with ANDAs that are not the reference listed product), revised labeling should be submitted based on the approved geriatric labeling of the reference listed drug product in the Orange Book when that drug's labeling is changed to include a *Geriatric Use* subsection.

² See 62 FR 45313 at 45319 for further clarification.

³ See 62 FR 45313 at 45316 for further clarification.

⁴ See *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book), FDA, sec. 1.4.

⁵ For drugs that are available as both OTC and prescription drug products, the holders of applications for the prescription drug products are responsible for submitting revised geriatric labeling.

Table 1. Categories for Revised Geriatric Labeling

Type of Drug Product	Submission
\$ Approved NDA and BLA marketed products \$ Approved ANDA marketed drug products where the ANDA is the reference listed drug in the publication <i>Approved Drug Products with Therapeutic Equivalence Evaluations</i> ^A	Revised labeling and supporting data as outlined in the geriatric labeling final rule
\$ Drug Products for which there is no approved application (e.g., pre-1938 drug products without an approved application) \$ Unmarketed drug products of approved NDA, BLA or ANDA ^B \$ OTC Drug Products	None
\$ Approved ANDA marketed drug products that are not the marketed reference listed drug	Revised labeling based on reference listed drugs <i>Geriatric Use</i> subsection

^A Some ANDA products may be designated as a reference listed drug solely because they have a different dosage form compared to the innovator product (e.g., tablet versus capsule) but their labeling still conforms to the innovator product labeling (i.e., changes in the NDA holder's (innovator's) labeling result in changes in the ANDA holder's labeling). For this situation, the ANDA holder is responsible for submitting a supplement providing any information regarding the use of its product in the elderly or to acknowledge that it has no information and it will conform to changes in the innovator's labeling. In cases where the ANDA is the reference listed drug and there is no marketed innovator drug product, the ANDA holder is responsible for submitting a *Geriatric Use* subsection.

^B If the application holder decides to resume marketing of a drug product, a geriatric labeling supplement should be submitted prior to marketing.

IV. IMPLEMENTATION OF THE GERIATRIC LABELING RULE

The geriatric labeling final rule (62 FR 45313) provides for staggered implementation dates for products approved prior to the effective date of the rule, August 27, 1998. Because certain classes of drugs were thought to pose potential problems for geriatric patients, labeling changes for these drugs were subject to priority implementation and were to be submitted to the FDA by August 27, 1998 (62 FR 45320). The Agency selected the following drug classes for priority implementation:

- Psychotropic drugs (antidepressants, anxiolytics, hypnotics, and antipsychotics)
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Digoxin, antiarrhythmics, and calcium channel blockers
- Oral hypoglycemic agents
- Anticoagulants
- Quinolones

For marketed drugs not in the priority categories, the implementation schedule is based on the year in which the drug product's new molecular entity (NME) (active moiety) or biological product license was first approved. Table 2 summarizes the dates for submitting geriatric labeling. Any application submitted after August 27, 1998, must include a *Geriatric Use* subsection in the proposed labeling (21 CFR 314.57(f)(10)). Sponsors of applications for new drug products currently under review should provide *Geriatric Use* subsections for their proposed labeling as an amendment to pending applications.

Table 2. Dates for Submitting Geriatric Labeling

Drug Categories	Type of Submission	Date
New Applications		
Applications submitted after August 27, 1998	NDA or BLA Submissions	\$ With application
Applications submitted after August 27, 1997, and before August 27, 1998	Amendment (if pending) Supplement (if approved)	\$ August 27, 1998
Marketed Priority Drugs^A		
NME first approved prior to August 27, 1998	Supplement	\$ August 27, 1998
Marketed Drugs Not on the Priority Implementation Schedule		
NME or biological product first approved from 1989 to August 27, 1997	Supplement	\$ August 27, 1999
NME or biological product first approved from 1982 through 1988	Supplement	\$ August 28, 2000
NME or biological product first approved from 1975 through 1981	Supplement	\$ August 27, 2001
NME or biological product first approved from 1963 through 1974	Supplement	\$ August 27, 2002
NME or biological product first approved prior to 1963	Supplement	\$ August 27, 2003

^A Priority Drugs are psychotropic drugs; nonsteroidal anti-inflammatory drugs (NSAIDs); digoxin, antiarrhythmics, and calcium channel blockers; oral hypoglycemic agents; anticoagulants; and quinolones. There are no priority biological products.

Holders of ANDAs designated as the reference listed drug in the Orange Book are responsible for submitting a geriatric labeling supplement provided their labeling does not conform to an innovator product's labeling. All holders of ANDAs that are not listed as the reference listed drug in the Orange Book should revise their labeling in accordance with the last approved labeling of the reference listed drug.⁶ If an ANDA holder receives a reference listed drug designation subsequent to the release of this guidance, it is the responsibility of that holder to supplement the application(s) in the manner described in the guidance.

V. DESCRIPTION OF REGULATION AND OPTIONAL STANDARD LANGUAGE

The geriatric labeling regulation (§ 201.57(f)(10)) includes six paragraphs ((i) through (vi)). These paragraphs outline various options for statements in the *Geriatric Use* subsection based on the type of information available and the interpretation of that information. In addition, paragraphs (ii)(A), (ii)(B) and (iii)(B) provide standard language to be used in the *Geriatric Use* subsection. A geriatric labeling supplement or amendment should include a cover letter that clearly indicates that the submission is for geriatric labeling and cites the specific paragraph(s) in the regulation that pertains to the labeling submitted. More than one paragraph may apply to a labeling submission. Table 3 summarizes the requirements of paragraphs (i) through (vi).

⁶ See the guidance for industry *Revising ANDA Labeling Following Revision of the RLD Labeling* (May 2000).

Table 3. Paragraphs (i) Through (vi) in 21 CFR 201.57(f)(10)

Paragraph in ' 201.57(f)(10)	Information in the Geriatric Use Subsection
(i)	A specific geriatric indication is included in the INDICATIONS AND USAGE section with more detailed discussion in appropriate sections (e.g., CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS).
(ii)	A statement on use in the geriatric population is included for the same indication approved for adults in general. The statement must reflect all relevant information available to the sponsor pertaining to use in the geriatric population and be one of the following three kinds.
(ii)(A)	Standard language for paragraph (ii) labeling if the clinical studies do not provide a sufficient number ^A of geriatric subjects to determine whether elderly respond differently.
(ii)(B)	Standard language for paragraph (ii) labeling if the clinical studies did include a sufficient number of geriatric subjects to determine whether elderly respond differently and no difference in response was detected.
(ii)(C)	If evidence from clinical studies and experience suggests that use in the elderly is associated with differences in safety or effectiveness, a brief description of the differences with reference to appropriate sections (e.g., CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS) in the labeling for more detailed discussion must be included.
(iii)(A)	Information from a pharmacokinetic or pharmacodynamic study performed in elderly subjects must be briefly described with reference to the appropriate sections (e.g., CLINICAL PHARMACOLOGY, DRUG INTERACTION, PRECAUTIONS) in the labeling for more detailed discussion.
(iii)(B)	Standard language for drugs that are substantially excreted ^B by the kidney.
(iv)	A statement describing a specific hazard with use of the drug in the elderly that references appropriate sections (e.g., CONTRAINDICATIONS, WARNINGS, PRECAUTIONS) in the labeling for more detailed discussion.
(v)	A statement that enhances safe use of the drug based on good clinical practice or past experience.
(vi)	If none of the requirements in (i) through (v) are appropriate or relevant to labeling, the sponsor must provide the reasons for the omission of the statements and may propose an alternative statement.

^A Fewer than 100 geriatric subjects. (See discussion in 62 FR 45313 at 45317.)

^B The final rule does not provide a definition for substantially excreted. (See discussion in 62 FR 45313 at 45318.)

Because there are currently no approved applications that have a specific geriatric indication, the FDA does not expect any application holders to submit geriatric labeling supplements under ' 201.57(f)(10)(i). Paragraph (i) pertains to future NDA or BLA submissions for a specific geriatric indication and to those applications currently under review. In either case, the review clock will not be reset because the data in support of geriatric labeling would be provided as part of an original submission or be submitted as an amendment to an NDA or BLA currently under review.

In cases where a drug product is unlikely to be used by the geriatric population, the application holder may submit a supplement under ' 201.57(f)(10)(vi) that requests omission of the *Geriatric Use* subsection or proposes an alternative statement with reasons supporting the request.

The geriatric labeling statements provided in the final rule are not applicable for most topical ophthalmic drug products. As a general rule, clinical differences in response between the geriatric and younger populations, from both an efficacy and safety perspective, have not been demonstrated to occur in clinical studies of topical ophthalmic drug products. The systemic absorption of topical ophthalmic drug products is usually minimal, and consequently, systemic interactions are unlikely and have been observed very infrequently. Where clinical differences between the geriatric and younger populations are not demonstrated, sponsors of new drug applications for topical ophthalmic drug products should request an alternative statement for the *Geriatric Use* subsection under ' 201.57(f)(10)(vi), such as “No overall differences in safety or effectiveness have been observed between elderly and younger patients.”

VI. CONTENT AND FORMAT

In the *Federal Register* of February 11, 1998 (63 FR 6854), FDA amended the NDA format and content regulations to require safety and effectiveness data for important demographic subgroups, including age subgroups (21 CFR 314.50(d)(5)(v) and (vi)(a)). The regulation, effective August 10, 1998, also amends IND regulations to require sponsors to tabulate in their annual reports the number of subjects enrolled to date in clinical studies for drug and biological products according to certain subgroups, including age (21 CFR 312.33(a)(2)).

All supplements submitted to comply with the geriatric labeling final rule should be noted as "Geriatric Labeling Supplement" in the "Reason for Submission" block on FDA Form 356h for submissions to CDER or CBER. The following information should be included in the supplement in the order shown.

A. Cover Letter C A cover letter should include the following information.

1. Indicate that the submission is a geriatric labeling supplement.
2. Specify the paragraph(s) of the regulation pertinent to the supplement.
3. Include the user fee identification number if applicable.
4. If no user fee is required, explain the reason for the exception.

B. Detailed Table of Contents

C. Revised Labeling

1. Include a draft of the revised labeling.⁷
2. Include a marked-up copy of the last approved labeling,⁸ clearly showing all additions and deletions,⁹ with annotations of where the supporting data are located in the submission.
3. Submissions to CBER should use form *FDA 2567 C Transmittal of Labels and Circulars*.

D. Applicable Regulatory Paragraph(s)

Indicate under which paragraph(s) in ' 201.57(f)(10) (i) through (vi) the labeling is being revised and explain how the regulation applies .

E. User Fee

If applicable, the appropriate user fee needs to be submitted (21 U.S.C. 379h) and should be sent to the designated bank. A user fee cover sheet (Form FDA 3397) should be included in each submission (OMB No. 0910-0297). If no user fee is applicable, the sponsor should so indicate on the user fee cover sheet. (See section VII.)

F. Data to Support Geriatric Use Labeling

Data by type (e.g., efficacy, pharmacokinetic/pharmacodynamic, safety) should be presented, analyzed, and summarized, including data taken from published literature, using applicable parts of the format described in the *Format and Content of the Clinical and Statistical Sections of New Drug Applications* (FDA 1988).¹⁰ In addition, the following points should be noted.

⁷ In the case where the applicant is submitting a supplement under § 201.57(f)(10)(vi) that requests omission of the *Geriatric Use* subsection or proposes an alternative statement, the applicant is required to include reasons to support the request.

⁸ Current labeling may differ from last approved labeling because the current labeling may include additions and/or deletions made before FDA approval (§ 314.70(c) or § 601.12(f)(2) and (3)) that have not yet undergone FDA review

⁹ Show all changes being effected under § 314.70(c) or § 601.12(f)(2) and (3) that have not received an approval letter at the time of the Geriatric Use submission. Annotations for these changes should include the date and serial number or reference of the submission. It is not necessary to resubmit the data or analysis that supported the change.

¹⁰ For additional information, consult the following International Conference on Harmonisation (ICH) guidances: *ICH E3 Structure and Content of Clinical Study Reports* (July 1996).

ICH M4 Common Technical Document. (In November 2000, ICH endorsed ICH M4, which describes the content and format of a common application (CTD) for new products (including biotechnology-derived products) for submission to regulatory authorities. The efficacy or clinical section (ICH M4E) contains information on study reports and key literature references. FDA published the draft ICH M4 guidance in August 2000. The final M4 guidance will be published in the coming months.)

1. The source of the data should be described (e.g., sponsor's clinical data, medical literature, MedWatch).
2. Safety data should include the extent of exposure, duration of exposure, and adverse events.
3. Labeling that simply relocates information already in the approved labeling does not require a re-analysis of the original data that supported this information.
4. The analysis and source data that support any change from the currently approved labeling for the use of the drug product in the geriatric population should be submitted. For some supplements, the amount of potentially relevant data may be quite voluminous. In these instances, it will usually be useful to contact the FDA division where the application resides to discuss which data should be submitted.
5. The submission should state how the medical literature was searched (e.g., Medline), the beginning and ending dates covered by the search (month/year to month/year), and the date(s) the search was performed. A complete listing of literature reports reviewed by the sponsor should be included.¹¹ A summary of each literature article is not necessary. Only those articles that support the labeling change should be summarized as outlined in the *Format and Content of the Clinical and Statistical Sections of New Drug Applications*, and a copy of the article should be included in the submission.¹² The FDA reviewer of the supplement may request copies of other literature articles included in the listing that are not provided in the submission.

¹¹ The listing should be formatted as outlined in *Annals of Internal Medicine*, 126:36-47, 1997. (See discussion on References, pp. 40-42.)

¹² For additional information, see the guidance for industry entitled *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products* (FDA, 1998).

VII. APPLICABILITY OF USER FEES TO GERIATRIC LABELING SUPPLEMENTS

The Prescription Drug User Fee Act of 1992 as amended by the Food and Drug Administration Modernization Act of 1997 provides no specific waivers of user fees for geriatric labeling supplements, although a supplement may qualify for a waiver based on one or more of the grounds for granting waivers listed in section 736(d) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 379h(d)). It is expected, however, that very few geriatric labeling supplements will require the payment of user fees because they will not require clinical data for approval, and only supplements for which clinical data are required for approval are assessed fees.

Manufacturers should contact the appropriate review division if there is any question regarding a specific submission. The review division will determine whether approval of a specific geriatric labeling supplement requires clinical data.¹³ Supplements that require clinical data are normally liable for user fees and, therefore, must be covered by either a fee or a waiver, unless otherwise excluded (section 736(a)(1) of the Act). Supplements that do not require clinical data are acceptable for consideration for filing without payment of a fee. Supplements that contain clinical data not required for approval because the supplement does not propose to modify statements in the existing approved labeling would generally not be assessed a user fee. For example, most ' 201.57(f)(10)(ii)(A) and (B) supplements would not pay a fee.

Supplements that lessen or remove WARNINGS, PRECAUTIONS, or CONTRAINDICATIONS relative to the geriatric population should be supported by data. If those data meet the definition of clinical data for purposes of assessing user fees, the supplement will likely be assessed a user fee.

VIII. QUESTIONS REGARDING 21 CFR 201.57(f)(10)

Questions regarding any aspect of the implementation of the geriatric labeling final rule that are not addressed in this guidance should be directed to CDER or CBER as follows:

- CDER Executive Secretariat at FAX 301-594-5493 or by mail to CDER Executive Secretariat, HFD-006, 5600 Fishers Lane, Rockville, Maryland 20857, or
- CBER, Office of Communication, Training and Manufacturers Assistance, HFM-40, CBER, FDA, 1401 Rockville Pike, Rockville, MD 20852-1448.

Questions regarding specific applications should be directed to the division where the application resides.

¹³ FDA recently published a draft guidance for industry entitled *Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees* (66 FR 11175, February 22, 2001). Until this guidance is issued in final form, questions concerning the definition of clinical data for user fee purposes should be directed to the User Fee Staff (CDER) at 301-594-2041.