Geriatric Information in Human Prescription Drug and Biological Product Labeling

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Eric Brodsky at 301-796-0855, or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

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)

September 2020
Labeling

Geriatric Information in Human Prescription Drug and Biological Product Labeling

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

and/or

Office of Communication, Outreach, and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, rm. 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010; Email: ocod@fda.hhs.gov
https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances

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)

September 2020
Labeling

TABLE OF CONTENTS

Geriatric Information in Human Prescription Drug and Biological Product Labeling Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to assist applicants of human prescription drug and biological products[2] in determining the appropriate placement and content of geriatric information in labeling as described in the regulations for the content and format of labeling for human prescription drug and biological products.[3,4]

The goal of this guidance is to provide recommendations to help ensure that appropriate information on the use of prescription drugs in geriatric patients is consistently placed in the proper sections and subsections within labeling so that the information is clear and accessible to health care practitioners and includes content that guides the safe and effective use in geriatric patients.

This guidance, which replaces the withdrawn guidance for industry *Content and Format for Geriatric Labeling* (October 2001), provides additional examples of geriatric use statements in labeling and examples of when the labeling regulations authorize the FDA to permit applicants to omit or revise specific information otherwise required in the *Geriatric Use* subsection.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of

[1] This guidance has been prepared by the Labeling Policy Team in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

[2] For the purposes of this guidance, references to *drugs* and *drug and biological products* include drugs approved under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) and biological products licensed under section 351 of the Public Health Service Act (42 U.S.C. 262) that are regulated as drugs.

[3] See 21 CFR 201.56(d) and 21 CFR 201.57.

[4] This guidance does not pertain to labeling for nonprescription drugs.

the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. Geriatric Initiatives

1. Geriatric Clinical Data Initiatives

In the 1980s, the FDA began several initiatives to increase the quantity and quality of information about the use of drugs in geriatric patients (defined as patients 65 years of age and older) so that health care practitioners would have enough information for the safe and effective use of drugs in geriatric patients. For example, the FDA encourages a thorough evaluation of the effectiveness and safety of drugs in geriatric patients and recommends examination of age-related differences in effectiveness, dose response, and safety.[5] In 1998, the FDA required new drug application (NDA) holders[6] and, subsequently, recommended that biologics license application (BLA) holders[7] present in their applications effectiveness and safety data based on age. In 2012, in an International Conference on Harmonisation (ICH) guidance for industry, the FDA reaffirmed the importance of obtaining geriatric data, across the entire full age range of the geriatric population because of the likelihood of comorbidities and the increasing number of geriatric patients in the United States.[8] The guidance also noted ways in which geriatric patients (especially patients 75 years of age and older) may respond differently to drug therapy than younger adult patients.[9]

In 2012, the Food and Drug Administration Safety and Innovation Act (FDASIA) directed the FDA to report on the inclusion of demographic subgroups (including age subgroups) in clinical

[5] See the guidance for industry *Guideline for the Study of Drugs Likely to Be Used in the Elderly* (November 1989) and the International Conference on Harmonisation guidance for industry *E7 Studies in Support of Special Populations: Geriatrics* (August 1994). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[6] See the preamble of the demographic rule (21 CFR 314.50(d)(5); 63 FR 6854) published February 11, 1998. In addition to age, NDA holders are required to present effectiveness and safety data in other important demographic groups in their NDAs.

[7] See the guidance for industry and FDA staff *Collection of Race and Ethnicity Data in Clinical Trials* (October 2016). In addition to age, the FDA recommends that BLA holders present effectiveness and safety data in other important demographic groups in their BLAs.

[8] See the ICH guidance for industry *E7 Studies in Support of Special Populations: Geriatrics: Questions and Answers* (February 2012).

[9] Ibid.

studies and the analysis of these demographic subgroups (including age subgroups) in NDAs and BLAs.[10]

2. Geriatric Labeling Initiatives

Until the late 1990s, the majority of drug labeling contained minimal or no geriatric use information to guide safe and effective use in the geriatric population. In 1997, the FDA issued a final rule creating a *Geriatric Use* subsection of labeling to promote the consistent inclusion of all relevant geriatric information in labeling.[11] This subsection is intended to provide information on possible differences in the safety, effectiveness, pharmacodynamics, and/or pharmacokinetics between geriatric and younger adult patients given differences in responses, drug elimination, comorbidities, organ function (e.g., renal function), consequences of adverse reactions, and concomitant therapy (e.g., higher risk of drug interactions because of polypharmacy).

In 2001, the FDA issued the now-withdrawn guidance for industry *Content and Format for Geriatric Labeling*, which provided recommendations for the *Geriatric Use* subsection in the PRECAUTIONS section. In 2006, the FDA issued the final rule "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*"* (commonly referred to as the physician labeling rule (PLR)), which relocated the *Geriatric Use* subsection from the PRECAUTIONS section in *old* (non-PLR) format labeling to the USE IN SPECIFIC POPULATIONS section for labeling required to be in PLR format.[12]

B. Geriatric Population in Labeling

In general, for prescription drug labeling, the adult population is defined as patients 17 years of age and older, and the geriatric population is defined as patients 65 years of age and older.[13] Therefore, information in labeling that is pertinent to the adult population is typically also pertinent to the geriatric population (e.g., indications approved *in adults* include geriatric patients).[14]

[10] See section 907 of FDASIA.

[11] See the preamble of the final rule, "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Addition of 'Geriatric Use' Subsection in the Labeling," (21 CFR 201; 62 FR 45313) published August 27, 1997, section II.A.

[12] See the preamble of the final rule, "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products," (21 CFR parts 201, 314, and 601; 71 FR 3922) published January 24, 2006.

[13] 21 CFR 201.57(c)(9)(iv)(A) and 21 CFR 201.57(c)(9)(v)(A).

[14] See the draft guidance for industry *Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (July 2018). When final, this guidance will represent the FDA's current thinking on this topic.

The information in the *Geriatric Use* subsection must pertain to the use of the drug in patients 65 years of age and older, unless otherwise noted.[15] Patients 65 years of age and older are not a homogeneous group (e.g., differences in organ function, comorbidities, concomitant drugs, and drug distribution and elimination). Applicants should include information on additional geriatric age subgroups in the labeling if important differences exist in responses in these subgroups.[16] Such subgroups should be further defined in the labeling as appropriate (e.g., 65-74 years of age; 75-84 years of age; and 85 years of age and older).[17] In some cases, geriatric age might be expressed as a continuous function of age.[18]

III. OVERVIEW OF GERIATRIC USE INFORMATION IN HUMAN PRESCRIPTION DRUG AND BIOLOGICAL PRODUCT LABELING

In general, applicants must summarize certain geriatric use information in the *Geriatric Use* subsection[19] and, when appropriate, must cross-reference the appropriate section(s) or subsection(s) of labeling that provide more detailed geriatric use information.[20] Certain geriatric use information must be included based on the type of information being conveyed,[21] which can be characterized as follows:

---

[15] 21 CFR 201.57(c)(9)(v)(A). See also the preamble of the final rule, "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Addition of 'Geriatric Use' Subsection in the Labeling," (21 CFR 201; 62 FR 45313, 45316) published August 27, 1997, stating that the Agency "does not consider 65 years of age to be an absolute" age cut-off to define geriatric patients in labeling. For some labeling, it may be more appropriate to choose a different age cut-off to define geriatric patients.

[16] See the preamble of the final rule, "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Addition of 'Geriatric Use' Subsection in the Labeling," (21 CFR 201; 62 FR 45313, 45316) published August 27, 1997.

[17] The FDA recommends that the age distribution in the clinical development program be representative of the target population, and that applications should assess the consistency of the treatment effect and safety profile in geriatric subpopulations (e.g., 65–74 years of age, 75–84 years of age, and 85 years of age and older) and younger adults. See the guidance for industry *E7 Studies in Support of Special Populations: Geriatrics: Questions and Answers*.

[18] See the preamble of the final rule, "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Addition of 'Geriatric Use' Subsection in the Labeling," (21 CFR 201; 62 FR 45313, 45316) published August 27, 1997.

[19] See 21 CFR 201.57(c)(9)(v). The FDA may permit omission of required statement(s) in the *Geriatric Use* subsection if the FDA determines that no statement described in 21 CFR 201.57(c)(9)(v)(A) to (E) is appropriate or relevant to the drug's labeling; additionally, the FDA may permit an alternative appropriate and accurate statement(s) (21 CFR 201.57(c)(9)(v)(F)).

[20] 21 CFR 201.57(c)(9)(v)(B)(3) and 21 CFR 201.57(c)(9)(v)(D). Additional cross-references from the *Geriatric Use* subsection to other section(s)/subsection(s) are recommended when there is more detailed geriatric use information in those other section(s)/subsection(s). See the guidance for industry *Labeling for Human Prescription Drug and Biological Products — Implementing the PLR Content and Format Requirements* (February 2013).

[21] See 21 CFR 201.57(c)(9)(v).

- Three scenarios (i.e., **scenarios 1.1, 1.2, and 1.3**) in which the drug is approved for use in adult patients generally, including geriatric patients or a subset of the geriatric population:

  - **Scenario 1.1:** When information is sufficient to detect differences in safety and/or effectiveness between geriatric and younger adult patients and there were no observed differences in safety and/or effectiveness between these groups[22]

  - **Scenario 1.2:** When information is sufficient to detect differences in safety and/or effectiveness between geriatric and younger adult patients and differences in safety and/or effectiveness between these groups were observed[23]

  - **Scenario 1.3**: When information is insufficient to detect differences in safety and/or effectiveness between geriatric and younger adult patients[24]

- **Scenario 2** in which the drug is approved for a geriatric-specific indication[25] (i.e., for a specific indication, the drug is indicated for use only in geriatric patients (or a subset of the geriatric population) and not in adult patients less than 65 years old).

The following sections provide more detailed descriptions of scenarios 1.1, 1.2, 1.3, and 2 and geriatric information that is required or recommended for inclusion in relevant sections and subsections of labeling.

IV. DRUG IS APPROVED FOR USE GENERALLY IN ADULT PATIENTS INCLUDING GERIATRIC PATIENTS OR A SUBSET OF THE GERIATRIC POPULATION (SCENARIOS 1.1, 1.2, AND 1.3)

A. Including Information in the Geriatric Use Subsection of Labeling (Scenarios 1.1, 1.2, and 1.3)

The *Geriatric Use* subsection must include certain information pertinent to the safe and effective use of the drug in geriatric patients for all indications approved for use in adult patients (including geriatric patients).[26]

[22] 21 CFR 201.57(c)(9)(v)(B)(2).

[23] 21 CFR 201.57(c)(9)(v)(B)(3).

[24] 21 CFR 201.57(c)(9)(v)(B)(1).

[25] 21 CFR 201.57(c)(9)(v)(A).

[26] 21 CFR 201.57(c)(9)(v)(B).

Information in this subsection is typically derived from results from controlled clinical studies submitted in the application or supplement(s) that are relevant to the use of the drug in geriatric patients. However, sometimes information in this subsection is obtained from "other reported clinical experience"[27] such as, but not limited to, well-documented studies obtained from a literature search, clinically relevant information from registries, other epidemiological or surveillance studies, case series studies, and adverse event reports.[28]

Under scenario 1.1, the *Geriatric Use* subsection must include the percentage of patients 65 years of age and older and the percentage of patients 75 years of age and older (or the total number of patients 65 years of age and older and the total number of patients 75 years of age and older) in the clinical studies of the drug.[29] Under this scenario, to provide more information to health care practitioners about geriatric exposure, the FDA recommends that this subsection present both the number and percentage of drug-exposed patients 65 years of age and older, and the number and percentage of drug-exposed patients 75 years of age and older in a defined group of clinical studies (typically the clinical studies that supported the approval of the drug in adult patients, including geriatric patients). Under scenario 1.1, alternative age cutoff point(s) within the geriatric population may be permitted to describe drug exposure, if the FDA determines that such age cutoff point(s) are accurate and appropriate.[30]

Under scenarios 1.2 and 1.3, the FDA recommends including geriatric exposure information in the *Geriatric Use* subsection. Specifically, we recommend that this subsection provide both the number and percentage of drug-exposed geriatric patients in a defined group of clinical studies (typically the clinical studies that supported the approval of the drug in adult patients, including geriatric patients). Different age cutoff points within the geriatric population can be selected to describe drug exposure, depending on the database (see section II.B., Geriatric Population in Labeling, in this guidance).

Under scenarios 1.1, 1.2, and 1.3, the *Geriatric Use* subsection can also include information on the total number of geriatric patients in the clinical studies (e.g., including drug-treated patients and control-treated patients). Under these scenarios, we recommend that this subsection cross-reference to other sections of labeling that contain additional details about the studies used to determine the geriatric exposure (e.g., the CLINICAL STUDIES section).

In general, geriatric exposure information should be placed at the beginning of the *Geriatric Use* subsection. However, information on specific risks or safety concerns associated with the use of the drug in geriatric patients and/or recommendations on specific monitoring in geriatric patients may appear before the drug exposure information.

---

[27] 21 CFR 201.57(c)(9)(v)(B)(1), (2), and (3).

[28] See the preamble of the final rule, "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Addition of 'Geriatric Use' Subsection in the Labeling," (21 CFR 201; 62 FR 45313) published August 27, 1997.

[29] 21 CFR 201.57(c)(9)(v)(B)(2).

[30] 21 CFR 201.57(c)(9)(v)(F).

The following examples represent options for summarizing geriatric exposure information under scenarios 1.1, 1.2, and/or 1.3; alternative language can be proposed.

- Example 1:

  "There were n patients 65 years of age and older in the clinical studies for Disease A *[see Clinical Studies (14)]*. Of the total number of DRUG X-treated patients in these studies, n (y%) were 65 years of age and older, while n (z%) were 75 years of age and older."

- Example 2:

  "Of the total number of DRUG X-treated patients in clinical studies for Disease A, n (y%) were 65 to 74 years of age, and n (z%) were 75 years of age and older *[see Clinical Studies (14)]*."

- Example 3:

  "There were n patients 65 years of age and older in the clinical studies for Disease A, Disease B, and Disease C *[see Clinical Studies (14.1, 14.2, 14.3)]*. Of the total number of DRUG X-treated patients in these studies, n (x%) were 65 to 74 years of age, n (y%) were 75 to 84 years of age, and n (z%) were 85 years of age and older."

1. When Information Is Sufficient to Detect Differences in Safety and/or Effectiveness Between Geriatric and Younger Adult Patients — Geriatric Use Subsection (Scenarios 1.1 and 1.2)

Factors that can affect whether there is sufficient information to detect differences in safety or effectiveness between geriatric and younger adult patients include the numbers of geriatric patients treated with the drug and control compared with the numbers of younger adult patients treated with the drug and control, the age distribution within the geriatric and younger adult subpopulations, the specific safety or effectiveness outcomes of interest, the magnitudes of differences in effects, and the variability in the outcomes. We recommend applicants contact the Agency if they have questions about whether there is sufficient information to detect differences in safety or effectiveness between geriatric and younger adult patients.

In general, integrated analyses of geriatric data from multiple studies can help increase the precision of safety and effectiveness evaluations and provide a more clinically useful representation of a drug's benefit-risk profile in geriatric patients. Determination of whether and how to include such integrated analyses in labeling should incorporate considerations about any differences in design or conduct between studies. The method for integration should appropriately account for the effect of differences in randomization ratios, patient populations,

and other factors across studies and use statistically appropriate methods for integrating data from multiple studies to minimize bias.[31]

a. No observed differences in safety and/or effectiveness in geriatric patients compared to younger adult patients (scenario 1.1)

If clinical studies included enough geriatric patients to make it likely that differences in safety or effectiveness between geriatric and younger adult patients 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 must contain the following statement after information about the percentage (or number) of geriatric patients (see section IV.A., Including Information in the Geriatric Use Subsection of Labeling (Scenarios 1.1, 1.2, and 1.3), of this gudiance):[32]

> "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."

An alternative statement may be permitted, if the FDA determines that such statement is accurate and appropriate.[33] Permissible changes may include, but are not limited to, the following:

- Using the term *patients* instead of *subjects*
- Using the term *younger adult patients* instead of *younger subjects* if safety and effectiveness comparisons were made between geriatric and younger adult patients (not pediatric patients)
- Removing the phrase "other reported clinical experience has not identified differences in responses between the elderly and younger patients" if there were no other clinical experience in geriatric patients (beyond the clinical study data submitted to support drug approval) because, for example, the drug is a new molecular entity that has never been marketed in any country
- Removing the phrase "but greater sensitivity of some older individuals cannot be ruled out" if this statement is inaccurate and/or clearly inapplicable for the drug[34]

[31] See the draft guidance for industry *Meta-Analyses of Randomized Controlled Clinical Trials to Evaluate the Safety of Human Drugs or Biological Products* (November 2018). When final, this guidance will represent the FDA's current thinking on this topic.

[32] 21 CFR 201.57(c)(9)(v)(B)(2).

[33] 21 CFR 201.57(c)(9)(v)(F).

[34] 21 CFR 201.56(a)(2) and 21 CFR 201.56(d)(4).

Such changes would result in an alternative statement such as the following:

> "No overall differences in safety or effectiveness of DRUG X have been observed between patients 65 years of age and older and younger adult patients."

For most topical ophthalmic drugs there have been no observed differences in safety or effectiveness between geriatric and younger adult patients in clinical studies. The systemic absorption of topical ophthalmic drugs is usually minimal, and consequently, systemic effects are unlikely and have been observed infrequently. Thus, when clinical differences between geriatric and younger adult patients have not been demonstrated, applicants of topical ophthalmic drugs may also use the alternative statement above.

b. Differences in safety and/or effectiveness in geriatric patients compared to younger adult patients (scenario 1.2)

The *Geriatric Use* subsection must contain a summary of observed differences or specific monitoring or dosage requirements in certain situations.[35] These situations occur when clinical studies and/or other reported clinical experience indicate that the use of the drug in geriatric patients, compared to its use in younger adult patients, is associated with differences in safety or effectiveness or requires specific monitoring or different recommended dosage in geriatric patients. For example, if geriatric patients experienced unique adverse reactions, adverse reactions occurred at a greater frequency or severity in geriatric patients than in younger adult patients, or there was reduced effectiveness in geriatric patients, this information must appear in the *Geriatric Use* subsection.[36] As appropriate, this information must also be included in other sections (e.g., DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, CLINICAL STUDIES).[37] For example:

> "The overall response rates in DRUG X-treated adult patients younger than 65 years of age, 65 years of age to younger than 75 years of age, and 75 years of age and older were 25%, 20%, and 15%, respectively. In comparison, the overall response rate for placebo-treated patients in each of these subgroups was 10%.
>
> In patients 65 years of age and older, consider premedication with drug 1, drug 2, and drug 3 before DRUG X use *[see Dosage and Administration (2.x)]*. In DRUG X-treated patients, the incidence of ≥ Grade 3 gastrointestinal (GI) adverse reactions (i.e., nausea and vomiting) was 10%, 35%, and 40% in adult patients younger than 65 years of age, 65 years of age to younger than 75 years of age, and 75 years of age and older, respectively *[see Adverse Reactions (6.1)]*. In comparison, in placebo-treated patients, ≥ Grade 3 GI adverse reactions (i.e., nausea and vomiting) occurred in 1–3% of patients in the three subpopulations."

[35] See 21 CFR 201.57(c)(9)(v)(B)(3).

[36] Ibid.

[37] Ibid.

2. When Information Is Insufficient to Detect Differences in Safety and/or Effectiveness Between Geriatric and Younger Adult Patients — Geriatric Use Subsection (Scenario 1.3)

If clinical studies did not include sufficient numbers of geriatric patients to determine whether geriatric patients respond differently than younger adult patients, and other reported clinical experience has not identified such differences, the *Geriatric Use* subsection must include the following statement (with respect to format, the FDA recommends this statement appear after the geriatric exposure information; see section IV.A., Including Information in the Geriatric Use Subsection of Labeling (Scenarios 1.1, 1.2, and 1.3), in this guidance):[38]

> "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."[39]

An alternative statement may be permitted, if the FDA determines that such statement is accurate and appropriate.[40] In addition to the permissible changes noted for scenario 1.1, additional changes may include, but are not limited to, the following:

- Defining the geriatric age group in the labeling

- Removing the following sentence if the drug has only one recommended starting dosage:

  "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."

Such changes would result in an alternative statement such as the following:

> "Clinical studies of DRUG X did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger adult patients."

When a drug is approved for adult patients (including geriatric patients) but there is limited or no experience in geriatric patients because the disease/condition primarily occurs in pediatric patients and/or younger adult patients (the disease/condition rarely occurs in geriatric patients)

---

[38] 21 CFR 201.57(c)(9)(v)(B)(1).

[39] Ibid

[40] 21 CFR 201.57(c)(9)(v)(F).

(e.g., Duchenne muscular dystrophy), the *Geriatric Use* subsection may contain the following or another appropriate and accurate alternative statement:

> "Disease A is largely a disease of pediatric and young adult patients. Clinical studies of DRUG X did not include patients 65 years of age and older."

If clinical studies primarily included geriatric patients and did not include sufficient numbers of younger adult patients to determine whether geriatric patients respond differently than younger adult patients, and there has been no other reported clinical experience in geriatric patients, we recommend that the *Geriatric Use* subsection contain a statement clarifying why there is insufficient information to detect differences in safety or effectiveness between geriatric and younger adult patients. The following is an example of such a statement in this situation:

> "Clinical studies of DRUG X did not include sufficient numbers of younger adult patients to determine if patients 65 years of age and older respond differently than younger adult patients."

3. Additional Required and Recommended Information in the Geriatric Use Subsection (Scenarios 1.1, 1.2, and 1.3)

a. Specific risks or safety concerns in geriatric patients — Geriatric Use subsection (scenarios 1.1, 1.2, and 1.3)

The *Geriatric Use* subsection must also include specific risks or safety concerns (hazards) associated with the use of the drug in geriatric patients and any need for specific monitoring, as well as other information related to the safe and effective use of the drug in the geriatric population.[41] If appropriate, the hazard must be summarized in the BOXED WARNING, CONTRAINDICATIONS, and/or WARNINGS AND PRECAUTIONS sections.[42] The following is an example of how to include information in the *Geriatric Use* subsection and cross-reference other relevant sections for a drug associated with greater sedation and delirium in geriatric patients compared to younger adult patients:

> "Because DRUG X-treated geriatric patients (patients 65 years of age and older) had a higher rate of sedation and delirium than control-treated geriatric patients (the rates were similar between DRUG X-treated and control-treated younger adult patients), initiate DRUG X at a lower dosage in geriatric patients *[see Dosage and Administration (2.x) and Warnings and Precautions (5.x)]*."

[41] 21 CFR 201.57(c)(9)(v)(A), (B)(3), and (D).

[42] 21 CFR 201.57(c)(9)(v)(D) and 21 CFR 201.57(c)(1), (5), and (6).

b. Summarizing specific pharmacokinetic or pharmacodynamic studies in geriatric patients — *Geriatric Use* subsection (scenarios 1.1, 1.2, and 1.3)

If specific pharmacokinetic or pharmacodynamic studies have been carried out in geriatric patients, they must be summarized in the *Geriatric Use* subsection and described in detail in the CLINICAL PHARMACOLOGY section[43] (the *Geriatric Use* subsection should include a cross-reference to the CLINICAL PHARMACOLOGY section). For the fictitious drug DRUG X (drugozide injection), examples of such statements in the *Geriatric Use* subsection include the following:

- Example 1:

  "Geriatric patients had higher plasma drugozide C_{max} and AUC compared to younger adult patients, and the plasma drugozide C_{max} and AUC observed in geriatric patients increases the risk of DRUG X-related adverse reactions *[see Warnings and Precautions (5.x) and Clinical Pharmacology (12.3)]*. Therefore, the recommended dosage of DRUG X in geriatric patients is lower than in younger adult patients *[see Dosage and Administration (2.x)]*."[44]

- Example 2:

  "No clinically meaningful differences in the pharmacokinetics of drugozide were observed in geriatric patients compared to younger adult patients *[see Clinical Pharmacology (12.3)]*."

c. When a drug is known to be substantially excreted by the kidney — *Geriatric Use* subsection (scenarios 1.1, 1.2, and 1.3)

If the drug is known to be substantially excreted by the kidney, the *Geriatric Use* subsection must include the following statement:[45]

> "This drug is known to be substantially excreted by the kidney, and the risk of adverse 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."

An alternative statement may be permitted, if the FDA determines that such statement is accurate and appropriate.[46] Permissible changes may include, but are not limited to, the following:

[43] 21 CFR 201.57(c)(9)(v)(C)(1).

[44] The term C_{max} refers to maximum plasma concentration. The term *AUC* refers to area under the curve.

[45] 21 CFR 201.57(c)(9)(v)(C)(2).

[46] 21 CFR 201.57(c)(9)(v)(F).

- Removing the phrase "risk of adverse reactions to this drug may be greater in patients with impaired renal function" if the risk of adverse reactions is the same in patients with renal impairment and in patients with normal renal function (e.g., the drug has a high therapeutic index).

- Using the term *geriatric patients* rather than *elderly patients.*

- Removing the following phrase if the drug has only one recommended dosage or if the labeling contains specific dosage recommendations for patients with renal impairment:

  "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."

- Removing the following phrase if the labeling includes specific recommendations for monitoring renal function or if for the specific drug or disease/condition it would not be useful to monitor for renal function:

  "It may be useful to monitor renal function."

Such changes would result in an alternative statement such as the following:

> "DRUG X is substantially excreted by the kidney, and the risk of adverse reactions to DRUG X may be greater in patients with renal impairment than in patients with normal renal function. Because geriatric patients are more likely to have renal impairment, monitor for Adverse Reactions Y and Z *[see Warnings and Precautions (5.x) and Use in Specific Populations (8.6)]*."

Alternatively, this statement can be omitted if it is clearly inapplicable or misleading[47] in the *Geriatric Use* subsection (e.g., the drug is contraindicated or not recommended for use in patients with moderate or severe renal impairment).[48]

If the drug is known to be substantially excreted by the kidney, the *Geriatric Use* subsection should, as appropriate, include a cross-reference to the *Renal Impairment* subsection (if any) in the USE IN SPECIFIC POPULATIONS section,[49] where clinically relevant details regarding use in patients with renal impairment would be included.

[47] See 21 CFR 201.56(a)(2) and 21 CFR 201.56(d)(4).

[48] In this example, information about the risks of use of the drug in patients with renal impairment would be described elsewhere in labeling (e.g., CONTRAINDICATIONS section, WARNINGS AND PRECAUTIONS section, *Renal Impairment* subsection in the USE IN SPECIFIC POPULATIONS section).

[49] See the draft guidance for industry *Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling* (March 2010). When final, this guidance will represent the FDA's current thinking on this topic.

B. Including Geriatric Use Information in Other Sections of Labeling (Scenarios 1.1, 1.2, and/or 1.3)

When the drug is approved for use generally in adult patients including geriatric patients (or a subset of the geriatric population), information about geriatric use may be required in other sections of the labeling. The following discusses both requirements and recommendations as to placement of geriatric use information in the relevant sections of labeling. The required and recommended information apply to scenarios 1.1, 1.2, and 1.3 unless otherwise noted.

- **INDICATIONS AND USAGE:** If a drug is indicated for use in the entire adult population (including geriatric patients), then in general, the term *adults* should be incorporated into the indication.[50] For example:

  "DRUG X is indicated for the treatment of Indication A in adults."

- **DOSAGE AND ADMINISTRATION:** Typically, the recommended dosage in geriatric patients is the same as the recommended dosage in younger adult patients. However, the DOSAGE AND ADMINISTRATION section must include the recommended dosage in geriatric patients if the recommended dosage in geriatric patients differs from the recommended dosage in younger adult patients.[51]

- **WARNINGS AND PRECAUTIONS:** Clinically significant adverse reactions or risks that are unique to geriatric patients must be included in the WARNINGS AND PRECAUTIONS section,[52] and clinically significant adverse reactions or risks that occur at a greater severity or frequency than in younger adult patients should generally also be included in this section (generally applies to scenario 1.2).[53]

- **ADVERSE REACTIONS:** If there are differences in the frequency, severity, or type of adverse reactions in geriatric patients compared to younger adult patients or if there are adverse reactions that are unique to geriatric patients, details of these adverse reaction data should be included in the ADVERSE REACTIONS section (generally applies to scenario 1.2).[54] However, if there are no differences in frequency (e.g., no differences in relative or absolute risk), severity, or type of adverse reactions in geriatric patients

[50] See the draft guidance for industry *Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (July 2018). When final, this guidance will represent the FDA's current thinking on this topic.

[51] See 21 CFR 201.57(c)(3)(C) and (H).

[52] See 21 CFR 201.57(c)(9)(v)(D) and 21 CFR 201.57(c)(6).

[53] See generally the guidance for industry *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format* (October 2011).

[54] See the guidance for industry *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2006).

compared to younger adult patients, it is not necessary to separately present adverse reactions from geriatric patients in this section (generally applies to scenarios 1.1 and 1.3).

- **CLINICAL PHARMACOLOGY:** The CLINICAL PHARMACOLOGY section must include detailed descriptions of pharmacokinetic and/or pharmacodynamic study data if such studies were carried out in geriatric patients[55] and should include relevant pharmacogenomic study data, data obtained from population analyses, and dose response information.[56]

- **CLINICAL STUDIES:** Clinical studies that provide substantial evidence of effectiveness for use of a drug in the geriatric population should be described in the CLINICAL STUDIES section (e.g., study design(s), population(s), endpoint(s), results and limitations of the study design or evidence).[57]

V. DRUG IS APPROVED FOR A GERIATRIC-SPECIFIC INDICATION (SCENARIO 2)

When a drug is approved for use for a geriatric-specific indication, the labeling must provide a summary of information essential for safe and effective use in geriatric patients.[58] The following describes both requirements and recommendations regarding placement of geriatric use information in relevant sections of labeling when a drug is approved for a geriatric-specific indication:

- **INDICATIONS AND USAGE:** All geriatric indications supported by adequate and well-controlled studies in geriatric patients must be included in the INDICATIONS AND USAGE section.[59] If the drug is indicated for use only in geriatric patients, in general, the FDA recommends using the phrases "patients XX years of age and older," "adults XX years of age and older," or similar phrases in the indication. For example:

  "DRUG X is indicated for the treatment of Indication A in patients 65 years of age and older."

[55] 21 CFR 201.57(c)(9)(v)(C)(1) and 21 CFR 201.57(c)(13).

[56] See the guidance for industry *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (December 2016).

[57] See the guidance for industry *Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2006).

[58] 21 CFR 201.56(a)(1).

[59] 21 CFR 201.57(c)(9)(v)(A).

- **DOSAGE AND ADMINISTRATION:** This section must include the recommended dosage in geriatric patients for all approved geriatric-specific indications.[60]

- **ADVERSE REACTIONS:** Geriatric adverse reaction data must be included in the ADVERSE REACTIONS section.[61]

- **USE IN SPECIFIC POPULATIONS, *Geriatric Use* subsection:** Only a summary statement of the approved geriatric indication(s) should be described in the *Geriatric Use* subsection. For example:

  "DRUG X is indicated in patients 65 years of age and older (for Indication A), and the information on this use is discussed throughout the labeling."

- **CLINICAL PHARMACOLOGY:** Data summarized in the *Geriatric Use* subsection must be discussed in more detail, if appropriate, in the CLINICAL PHARMACOLOGY section.[62] Detailed descriptions of geriatric pharmacokinetic, pharmacodynamic, and/or pharmacogenomic study data; relevant data obtained from population analyses; and dose response information should be included in this section.[63]

- **CLINICAL STUDIES:** Data summarized in the *Geriatric Use* subsection must be discussed in more detail, if appropriate, in the CLINICAL STUDIES section.[64] Detailed descriptions of studies that provide substantial evidence of effectiveness for use in geriatric patients (e.g., study design(s), population(s), endpoint(s), results and limitations of the study design or evidence) should be provided in this section.[65]

VI. DRUG IS NOT APPROVED IN THE GERIATRIC POPULATION

Drugs that are studied only in younger adult patients (not geriatric patients) are typically approved for all adult patients (including geriatric patients) because of generalizability of the evidence to geriatric patients, consistencies in the disease processes across geriatric and younger adults, and the drug's overall benefits and risks. However, there are uncommon situations when the evidence does not support the use of a drug in a geriatric population because clinical studies

[60] 21 CFR 201.57(c)(3)(C) and 21 CFR 201.57(c)(9)(v)(A).

[61] 21 CFR 201.57(c)(7).

[62] 21 CFR 201.57(c)(9)(v)(A) and 21 CFR 201.57(c)(9)(v)(C)(1).

[63] See the guidance for industry *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Format*. See also 21 CFR 201.57(c)(13).

[64] 21 CFR 201.57(c)(9)(v)(A).

[65] See the guidance for industry *Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products — Content and Format*. See also 21 CFR 201.57(c)(15).

did not include a sufficient number of geriatric patients to support geriatric use for an indication.[66] Additionally, there are uncommon situations when the evidence does not support the use of a drug in a geriatric population because the results of studies conducted in a geriatric population strongly suggest that the drug is ineffective or the benefit-risk profile is unfavorable (but the evidence falls short of warranting a contraindication).[67]

We recommend applicants contact the Agency if they have questions about developing labeling for these uncommon situations.

If the use of the drug in geriatric patients is associated with a risk or safety concern (hazard) in geriatric patients, the risk or safety concern must be described in the *Geriatric Use* subsection or, if appropriate, must be stated in the CONTRAINDICATIONS and/or WARNINGS AND PRECAUTIONS section(s), and the *Geriatric Use* subsection must cross-reference the section or sections, if appropriate.[68] Any such hazard must be stated in other sections of labeling (e.g., BOXED WARNING), as appropriate.[69]

VII. OMITTING OR REVISING INFORMATION AND UPDATING LABELING

If an applicant believes that none of the requirements described in 21 CFR 201.57(c)(9)(v)(A) to (E) is appropriate or relevant to its drug's labeling, the applicant must provide a rationale for omission of the statement(s) and may propose an alternative statement.[70] The FDA may permit omission of such statement(s) or alternative appropriate and accurate statement(s) if the FDA determines that no statement(s) described in 21 CFR 201.57(c)(9)(v)(A) to (E) are appropriate or relevant to the drug's labeling.[71] In some circumstances, applicants should omit specific information otherwise required in the *Geriatric Use* subsection or omit the entire subsection because the information is clearly inapplicable; applicants must omit such specific information or

[66] These situations are different from situations when the entire *Geriatric Use* subsection is omitted because the information is clearly inapplicable or misleading (see section VII., Omitting or Revising Information and Updating Labeling).

[67] Ibid.

[68] 21 CFR 201.57(c)(9)(v)(D).

[69] The BOXED WARNING section requires that certain contraindications or serious warnings may be required by the FDA to be presented in a box (21 CFR 201.57(c)(1)). The WARNINGS AND PRECAUTIONS "section must describe clinically significant adverse reactions (including any that are potentially fatal, are serious even if infrequent, or can be prevented or mitigated through appropriate use of the drug), other potential safety hazards" (21 CFR 201.57(c)(6)(i)). The CONTRAINDICATIONS "section must describe any situations in which the drug should not be used because the risk of use (e.g., certain potentially fatal adverse reactions) clearly outweighs any possible therapeutic benefit … Known hazards and not theoretical possibilities must be listed" (21 CFR 201.57(c)(5)).

[70] 21 CFR 201.57(c)(9)(v)(F).

[71] Ibid.

584 the entire subsection if it is misleading.[72] For example, if a drug is indicated for use only in
585 neonates, the applicant should omit the *Geriatric Use* subsection because this subsection is
586 clearly inapplicable. We recommend applicants contact the Agency if they have questions about
587 omitting certain regulatory statements in the *Geriatric Use* subsection.
588
589 Labeling must be updated when new information becomes available that causes the labeling to
590 become inaccurate, false, or misleading.[73] Consistent with this requirement, when revising
591 existing information in the labeling, applicants should evaluate labeling content to ensure that it
592 accurately reflects current knowledge about the use of the drug in geriatric patients for all
593 approved indications. Applicants should evaluate available results from postmarketing
594 controlled clinical studies, well-documented studies obtained from a literature search that are
595 available to the applicant and reasonably relevant to the use of the drug in geriatric patients,
596 pharmacokinetic and pharmacodynamic studies conducted in geriatric patients, and adverse
597 event reports.[74] Applicants should review and update sections of labeling pertinent to the
598 geriatric use information as necessary when updating the labeling.

[72] Under 21 CFR 201.56(a)(2), "labeling must be informative and accurate and neither promotional in tone nor false or misleading." Under 21 CFR 201.56(d)(4), "[o]mit clearly inapplicable sections, subsections, or specific information." For additional information on omitting information in labeling, see the guidance for industry *Labeling for Human Prescription Drug and Biological Products — Implementing the PLR Content and Format Requirements* (February 2013).

[73] 21 CFR 201.56(a)(2).

[74] See 21 CFR 201.57(c)(9)(v)(B), which requires that such information be reflected in the *Geriatric Use* subsection.