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The Honorable Edward M. Kennedy
Chairman
Committee on Health, Education, Labor, and Pensions
United States Senate

The Honorable Henry A. Waxman
Chairman
Committee on Oversight and Government Reform
House of Representatives

Subject: *Prescription Drugs: FDA Guidance and Regulations Related to Data on Elderly Persons in Clinical Drug Trials*

Elderly persons use drugs at a higher rate than younger persons,¹ in part because elderly persons experience higher rates of certain diseases—such as cancer, Parkinson’s disease, and heart disorders. Elderly persons—those age 65 and older—are also more likely than younger adults to experience complications when taking some prescription drugs.² For example, because of their decreased liver and kidney functions, elderly persons often lack the ability to eliminate drugs from their bodies as efficiently as younger adults, making elderly persons more likely to experience side effects associated with drugs. As a result, the Food and Drug Administration (FDA) has noted that it is important that drugs be studied for use by elderly persons during the clinical drug trials³—that is, those drug studies conducted by drug sponsors before they submit an application to have a drug approved for marketing.⁴

¹National Center for Health Statistics, *Health, United States, 2006 With Chartbook on Trends in the Health of Americans* (Hyattsville, Md.: 2006).

²For purposes of geriatric drug labeling, the Food and Drug Administration has defined the geriatric or elderly population as persons age 65 and older. 62 *Fed. Reg.* 45313, 45316, 45325 (Aug. 27, 1997) (codified at 21 C.F.R. § 201.57(c)(9)(v) (2007)).

³Clinical drug trials are the studies conducted to demonstrate the safety and effectiveness of drugs in humans. Clinical drug trials generally include persons being treated with the drug against a comparison group. A comparison group may include participants who receive a placebo or nontherapeutic treatment or participants who receive an alternative therapy.

⁴Drug sponsors are usually pharmaceutical companies. In addition to pharmaceutical companies, other entities sponsoring drug development include government agencies, health care institutions, and individual physician investigators.

FDA is responsible for oversight of clinical drug trials and deciding whether to approve new drugs for marketing in the United States. This responsibility includes determining if drugs are safe and effective for the people expected to use them, including elderly persons. To implement its responsibilities, FDA issues guidance and regulations for drug sponsors on conducting clinical drug trials and submitting new drug applications (NDA) to FDA to seek drug approval based in part on the results of those clinical drug trials.⁵ NDAs include data on both the safety and effectiveness of the drug being studied. FDA guidance describes the process FDA medical officers (typically doctors) are to follow in reviewing those NDAs as part of the NDA review process and recommending whether to approve a new drug for marketing in the United States.⁶ As part of the process by which drugs are considered for approval, medical officers also meet in teams with supervisors and other experts, including biochemists and statisticians, to discuss the merits of the NDA.

Concerns have been raised about the inclusion of elderly persons in clinical drug trials.⁷ You asked us to examine FDA's activities related to data reported about elderly persons in the study of new drugs. In this report, we examine FDA's guidance and regulations related to (1) drug sponsors' reporting of data to FDA to describe the effects of a proposed drug on elderly persons and (2) FDA medical officers' review of safety and effectiveness data that drug sponsors provided for elderly persons.

To examine guidance and regulations on drug sponsors' reporting of data related to elderly persons, we reviewed FDA guidance related to the study of drugs and the format and content of an NDA. We also examined FDA regulations on reporting drug safety and effectiveness data by age in the NDA and reporting data on elderly persons on the drug labeling.⁸ To determine how drug sponsors have reported data related to the guidance and regulations, we reviewed all 36 NDAs submitted to FDA from January 1, 2001, through June 30, 2004, that FDA had reviewed and were for drugs that are proposed to treat diseases that we determined affect elderly persons with a disproportionately greater frequency compared to younger

⁵FDA issues both guidance and regulations relevant to the study of new drugs. Guidance describes the agency's policy on regulatory issues, thereby suggesting ways that drug sponsors or agency officials might meet those requirements that are specified in regulations.

⁶In this report, we use the term "guidance" to mean those FDA documents which outline procedures medical officers are to follow in their review.

⁷For example, see Lilia Talarico et al., "Enrollment of Elderly Patients in Clinical Trials for Cancer Drug Registration: A 7-Year Experience by the US Food and Drug Administration," *Journal of Clinical Oncology*, vol. 22, no. 22 (2004); Susan L. Mitchell et al., "Exclusion of Elderly Subjects from Clinical Trials for Parkinson Disease," *Archives of Neurology*, vol. 54, no. 11 (1997); and Patrick Y. Lee et al., "Representation of Elderly Persons and Women in Published Randomized Trials of Acute Coronary Syndromes," *Journal of the American Medical Association*, vol. 286, no. 6 (2001).

⁸The drug labeling includes the physician package insert, which is designed for and directed to physicians and other health care professionals and provides 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 (21 C.F.R. § 201.100(c)(1) (2007)). Among other things, drug labeling also includes the label—the printed information on the immediate container of the drug product—and the patient package inserts, which FDA also approves, designed to instruct patients about the safe and effective use of a drug.

persons.⁹ To determine the number of elderly participants associated with each NDA, we reviewed the overall descriptions of the clinical drug trials. To determine how drug sponsors reported safety and effectiveness data by age, we reviewed other sections of NDA summary documents that reported the relevant analyses.¹⁰

To examine the guidance for medical officers' review of data on elderly persons, we reviewed the most recent guidance (issued in 2004 and 2005) specifically for FDA medical officers and interviewed FDA officials responsible for overseeing the NDA review process to obtain information on how this guidance relates to the larger NDA review process. We also examined the FDA medical officer reviews completed for the 36 NDAs in our sample to obtain examples of examinations related to elderly persons. (See enc. I for a more detailed discussion of our scope and methodology.) We conducted our work from August 2004 through September 2005, in April 2006, and from April 2007 through September 2007, in accordance with generally accepted government auditing standards.

Results in Brief

FDA guidance recommends that drug sponsors include elderly persons in clinical drug trials, and FDA regulations require that the drug sponsors report clinical drug trial data by age. The agency guidance recommends that drug sponsors avoid excluding persons from clinical drug trials on the basis of advanced age and offers various suggestions on how drug sponsors should report the age of clinical drug trial participants to help FDA determine the number of elderly participants. To identify differences in the safety and effectiveness of a drug associated with age, FDA regulations require that drug sponsors report clinical drug trial data by age. For the 36 NDAs we reviewed, drug sponsors generally included elderly persons and reported safety and effectiveness data for elderly persons in clinical drug trials. FDA officials are developing guidance that would combine information currently available in multiple guidance documents on the format drug sponsors should use for reporting safety data in an NDA, including data about age.

FDA guidance recommends that medical officers determine whether the proposed drugs are safe and effective for the populations expected to use them, but the guidance does not mention elderly persons specifically. FDA officials told us that the agency expects that medical officers will assess the safety and effectiveness of a drug for elderly persons when they review data in an NDA; however, these expectations are not conveyed in agency guidance. We found that about two-thirds of the medical officer reviews we examined included a discussion by the medical officer of the safety and effectiveness of the drug for elderly persons. However, agency guidance does not direct medical officers to report whether sufficient numbers of elderly persons participated in NDA clinical drug trials to assess the safety and effectiveness of a drug for elderly persons. We found that about one-quarter of the medical officer clinical review summaries that we reviewed documented the medical officer's review of the sufficiency of representation of elderly persons. FDA officials told us that the agency's reviewers understand that the request in agency guidance for an analysis of a drug's effects by age includes an analysis of the drug's effects upon elderly

⁹Based on information provided by FDA officials in April 2007 that guidance and regulations related to elderly persons in clinical drug trials had not changed since the beginning of our review, we determined that these data were relevant for our purposes.

¹⁰A drug sponsor sometimes used different age categories to report summary information about participants, comparisons of safety by age, and comparisons of effectiveness by age.

persons. They also said that age differences are almost always discussed during team meetings. FDA officials added that approval recommendations are not made independently by one medical officer, but rather result from discussions among medical officers and others on a review team.

In commenting on a draft of this report, the Department of Health and Human Services (HHS) raised three main concerns. First, HHS stated that the draft did not completely summarize FDA's long-standing and extensive efforts to assure reasonable representation of elderly persons in clinical drug trials. As we noted in the draft report, FDA has made numerous efforts related to the inclusion of elderly persons in clinical drug trials and issued many related guidance documents. Further discussion of these issues was beyond the scope of this report. Second, HHS stated that we were incorrect in finding that agency guidance does not direct medical officers to report whether sufficient numbers of elderly persons are represented in NDA clinical drug trials. Such information is necessary for FDA to assess the safety and effectiveness of the drug for elderly persons. However, as we stated in the draft report and HHS noted in its comments, sufficiency of representation is referred to in FDA guidance using broad terms, such as "age" or "demographic subgroups," rather than using specific ages or terms such as "elderly." Only about one-quarter of the medical officer's clinical review summaries that we examined documented the medical officer's review of the sufficiency of representation of elderly persons. Third, HHS stated that we were critical of FDA for not adequately conveying to its reviewers the agency's expectations with regard to the need to review safety and effectiveness data related to elderly persons. However, we found that analyses of safety and effectiveness for elderly persons were documented in only about two-thirds of the medical officer reviews that we examined.

Background

FDA approves prescription drugs for marketing in part based on its determination that they are safe and effective for their intended use. Elderly persons sometimes react to drugs differently than younger persons. Determining safety and effectiveness for elderly persons requires that sufficient numbers of such participants be included in clinical drug trials. However, including elderly persons in clinical drug trials can sometimes be challenging.

The Drug Development and Approval Process

FDA helps to ensure the safety and effectiveness of marketed drugs by reviewing proposals for conducting clinical drug trials, reviewing drug applications and proposed drug labeling,¹¹ and monitoring the safety and effectiveness of drugs after they are marketed. Before any new drug can be tested on people, the drug sponsor generally must submit to FDA a proposal that, among other things, lays out a plan for how the drug will be tested and outlines the measures that will be taken to protect clinical drug trial participants.¹² This proposal is also required to

¹¹In response to concerns associated with the use of drugs by elderly persons, FDA began requiring a "geriatric use" subsection to a drug's labeling in 1998 (62 *Fed. Reg.* 45313, 4325 (Aug. 27, 1997)) (codified at 21 C.F.R. § 201.57(c)(9)(v) (2007)). This subsection of the drug labeling is where information related to a drug's safety and effectiveness for elderly persons is included by the drug sponsor.

¹²A narrow category of clinical drug trials in humans can be exempt from this requirement. See 21 C.F.R. § 312.2(b) (2007).

specify criteria that will be used to exclude persons from participating in clinical drug trials.¹³ For example, participants with other diseases or those taking certain other medications might be excluded from a clinical drug trial. Typically, a drug sponsor and FDA officials will have discussions about the design of the clinical drug trials before the drug sponsor submits this proposal.

To obtain approval for marketing a drug in the United States, drug sponsors must then submit information to FDA about the completed clinical drug trials—along with pharmacology and toxicology data, chemistry and manufacturing data, and proposed labeling language—in the form of an NDA. NDAs include sections summarizing safety and effectiveness data. FDA regulations require that these sections include background information about the clinical drug trials and summary information about their participants—including exclusion criteria used in the clinical drug trials—as well as evidence from clinical drug trials demonstrating that the proposed drug is safe and effective for its intended use.¹⁴ The NDAs are reviewed by FDA medical officers, typically doctors, who then discuss their reviews in teams with supervisors and other experts to help FDA determine whether to approve a drug for marketing.

Elderly Persons in Clinical Drug Trials

Assessing whether a drug is safe and effective for use by elderly persons requires that a sufficient number of elderly persons be included in clinical drug trials. As the number of elderly participants in clinical drug trials increases, the ability of drug sponsors to detect responses unique to elderly persons for a given safety or effectiveness outcome also increases. Failing to include sufficient numbers of elderly persons in clinical drug trials may make it less likely that safety concerns and effectiveness outcomes unique to elderly persons will be detected during the clinical drug trials.

A variety of factors make it difficult to include elderly persons in clinical drug trials. For example, elderly persons are more likely than younger persons to use multiple medications or have multiple diseases, which might preclude their participation in a clinical drug trial because these factors can confound the interpretation of the clinical drug trial results.¹⁵ Another challenge to including elderly persons in clinical drug trials is that some physicians might not refer elderly persons to clinical drug trials because they believe that elderly persons may be less likely than younger adults to tolerate or benefit from new drug therapies.¹⁶ Elderly persons might also avoid clinical drug trials if they believe the treatment would not benefit them or if they are concerned about the toxicity of the treatment.¹⁷

¹³21 C.F.R. § 312.23(a)(6)(iii)(c) (2007).

¹⁴See for example, 21 C.F.R. § 314.50(d)(5) (2007).

¹⁵Institute of Medicine, *Pharmacokinetics and Drug Interactions in the Elderly and Special Issues in Elderly African-American Populations* (Washington, D.C.: 1997).

¹⁶Edward L. Trimble et al., “Representation of Older Patients in Cancer Treatment Trials,” *Cancer Supplement*, vol. 74, no. 7 (1994).

¹⁷Joy H. Lewis et al., “Participation of Patients 65 Years of Age or Older in Cancer Clinical Trials,” *Journal of Clinical Oncology*, vol. 21, no. 7 (2003), and Trimble et al., “Representation of Older Patients in Cancer Treatment Trials.”

Elderly persons may also have difficulty accessing clinical drug trials. For example, elderly persons are more likely than younger adults to be affected by dementia and other cognitive impairments that can impede drug sponsors' ability to obtain their informed consent, which is necessary for participation in clinical drug trials.¹⁸ Elderly persons also may not want to or be able to participate in clinical drug trials. For example, participants in clinical drug trials may have to visit the doctor more often than they otherwise would, and elderly persons may have difficulty traveling to clinic appointments or may not be able to afford the necessary transportation costs.¹⁹

FDA's guidance recommends that drug sponsors not exclude elderly persons from clinical drug trials on the basis of their age alone because such exclusions might prevent drug sponsors from collecting sufficient information about the effects of drugs in elderly persons.²⁰ Instead, the guidance suggests that, when necessary, exclusion criteria should focus on more relevant issues, such as either the presence of an illness that could make participation in the clinical drug trial dangerous or the person's inability to provide informed consent.

FDA Guidance Encourages Inclusion of Elderly Persons, and Regulations Require That Drug Sponsors Report Clinical Drug Trial Data by Age

FDA guidance recommends that drug sponsors include elderly persons in clinical drug trials, and FDA regulations require that the drug sponsors report clinical drug trial data by age. Agency guidance recommends that drug sponsors avoid excluding persons on the basis of advanced age. To help FDA determine the number of elderly persons in clinical drug trials, agency guidance also recommends how drug sponsors should report the age of clinical drug trial participants in their NDAs and the various formats that drug sponsors can use to report this information. For example, FDA recommended in its current guidance on the format of a drug application, issued in 1988, various ways that drug sponsors could report the age of participants, including the average age, the ages of the youngest and oldest participants (the age range), and the number of participants who fall into specific age categories.²¹ In addition, FDA encourages meetings between drug sponsors and FDA officials prior to the submission of an NDA that may include discussions of the best approach for presenting and formatting data in the NDA.

¹⁸Institute of Medicine, *Pharmacokinetics and Drug Interactions in the Elderly and Special Issues in Elderly African-American Populations*.

¹⁹Erin L. Cassidy, E. Baird, and Javaid I. Sheikh, "Recruitment and Retention of Elderly Patients in Clinical Trials," *American Journal of Geriatric Psychiatry*, vol. 9, no. 2 (2001), and M. Margaret Kemeny et al., "Barriers to Clinical Trial Participation by Older Women With Breast Cancer," *Journal of Clinical Oncology*, vol. 21, no. 12 (2003).

²⁰Food and Drug Administration, *Guideline for the Study of Drugs Likely to be Used in the Elderly* (Rockville, Md.: November 1989), and *Studies in Support of Special Populations: Geriatrics* (Rockville, Md.: August 1994).

²¹Food and Drug Administration, *Guideline for the Format and Content of the Clinical and Statistical Sections of an Application* (Rockville, Md.: July 1988).

Based on summary information about the participants, we found that elderly persons were included in at least one clinical drug trial supporting each of the 36 NDAs we reviewed.²² For 28 NDAs, we were able to determine the number of elderly participants in at least one of the clinical drug trials. In the remaining 8 NDAs, we could not determine the exact number of elderly participants in any of the clinical drug trials because of the way that drug sponsors sometimes reported age data in the NDA (see enc. II). For example, an NDA may have reported only the age range of participants—such as from 18 through 91—rather than using the age category of 65 and older. This would indicate that there was at least one elderly person, but precluded us from determining the exact number of elderly participants.

FDA issued regulations in 1998 to require that drug sponsors report data from clinical drug trials that would identify differences in safety and effectiveness associated with age.²³ FDA has not developed guidance specifically including categories for elderly persons in these age comparisons, but FDA officials told us that drug sponsors know that age comparisons would include elderly persons and that elderly is defined as age 65 and older.²⁴ FDA officials are developing guidance that would combine information currently available in multiple guidance documents on the format drug sponsors should use for reporting safety data in an NDA, including data about age. In our review of 36 NDAs, we found that most drug sponsors used the age category of 65 and older when reporting on a drug’s safety and effectiveness by age (see enc. III).²⁵

FDA Expectations That Medical Officers Review Safety and Effectiveness Data Related to Elderly Persons Are Not Conveyed in Agency Guidance

FDA expectations that medical officers review safety and effectiveness data related to elderly persons are not conveyed in agency guidance. FDA’s guidance for evaluating safety and effectiveness refers to age subgroups broadly.²⁶ For example, FDA guidance states that it may be appropriate to examine whether there are differences in the safety and effectiveness of drugs between demographic subgroups, such as “old” and “young” participants. Guidance also specifies that the medical officers’ clinical review summaries should include an examination of safety and effectiveness data among clinical drug trial participants in various

²²NDAs often include data from more than one clinical drug trial.

²³63 *Fed. Reg.* 6854, 6862 (Feb. 11, 1998) (codified at 21 C.F.R. § 314.50(d)(5)(v), (vi)(a); § 312.33(a)(2) (2007)).

²⁴The preamble to the regulation states that, for the purposes of geriatric labeling, FDA has previously defined the “elderly” as persons age 65 years and older and recommends that drug sponsors use that definition for analysis of safety and effectiveness data for elderly persons (see 63 *Fed. Reg.* 6854, 6859 (Feb. 11, 1998)).

²⁵A drug sponsor sometimes used different age categories to report summary information about participants, comparisons of safety by age, and comparisons of effectiveness by age. As a result, the number of NDAs for which we could determine the number of elderly participants varies according to the data reported in each NDA.

²⁶FDA guidance documents for medical officers include a Clinical Review Template, introduced in July 2004, and guidance for reviewing NDA safety data, introduced in 2005. Agency officials told us that they intend to develop additional guidance specifically for the review of effectiveness studies. FDA guidance also includes Food and Drug Administration, *Reviewer Guidance: Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review* (Rockville, Md.: February 2005).

subgroups—such as age, gender, and race. In contrast, FDA guidance is more specific in its references to other demographic subgroups. For example, one guidance document dedicates specific subsections to how medical officers should include in their summaries examinations of data on the possible effects a drug may have for pregnant women and for children, but there is no similar subsection for elderly persons.²⁷

FDA officials responsible for overseeing the NDA review process told us that they believe that the agency’s reviewers understand that FDA guidance calling for an analysis of age, or information on special populations or demographic subgroups, also applies to elderly persons. Agency officials added that age-related differences are almost always part of the team discussions about NDAs held by medical officers when deciding whether to recommend a drug for approval. We found that about two-thirds of the medical officer reviews of the 36 NDAs that we examined included documentation of the medical officer’s review of safety or effectiveness data for persons age 65 and older.

FDA guidance does not suggest that medical officers determine whether sufficient numbers of elderly persons participated in NDA clinical drug trials, in order for FDA to assess the safety and effectiveness of the drug for elderly persons. Further, FDA guidance does not suggest that they document in their clinical review summaries the methods they used to determine whether sufficient numbers of elderly persons participated in NDA clinical drug trials. We found that about one-quarter of the medical officer clinical review summaries that we reviewed documented the medical officer’s review of the sufficiency of representation of elderly persons. None of these medical officer reviews documented the methods used by medical officers to make a determination of sufficiency. Nevertheless, FDA officials told us that medical officers routinely make such determinations. FDA officials told us that medical officers discuss their reviews in team meetings and that medical officers may conduct additional meetings to discuss the content of NDAs. Agency officials added that age-related differences are almost always part of the discussions within medical review teams that are held as part of the drug approval process.

Agency Comments and Our Evaluation

We provided a draft of this report to HHS for comment. In its comments, HHS raised three principal concerns. First, HHS stated that the draft did not completely summarize FDA’s long-standing and extensive efforts to assure reasonable representation of elderly persons in clinical drug trials. Second, HHS stated that we were incorrect in finding that agency guidance does not direct medical officers to report whether sufficient numbers of elderly persons participated in NDA clinical drug trials. Such information is necessary for FDA to assess the safety and effectiveness of the drug for elderly persons. Third, HHS stated that we were critical of FDA for not adequately conveying to its reviewers the agency’s expectations with regard to the need to review safety and effectiveness data related to elderly persons and that they disagreed with this criticism.

As we noted in the draft report, FDA has made numerous efforts related to the inclusion of elderly persons in clinical drug trials and issued many related guidance documents. Providing a detailed history of FDA’s work in this area was beyond the scope of this report.

²⁷FDA’s guidance includes a subsection where medical officers should report any available information on drug exposure to pregnant women and a subsection that should discuss the drug’s effects on growth in children, including the measurement of height and weight, the measurement methodology used, and adjustments for children’s age and gender, as appropriate.

In its comments, HHS referred to FDA’s guidance—the Clinical Review Template and its 2005 clinical safety review guidance—which HHS stated directs medical officers to report whether sufficient numbers of elderly persons participated in NDA clinical drug trials. However, all of the agency’s examples illustrate the broad references found in FDA guidance, such as “population studied,” “special populations,” “appropriate demographic subsets of patients,” “various demographic subjects,” and “age.” They do not refer specifically to any age group or terms such as “elderly.” FDA officials have told us, and the HHS comments stated, that medical officers know that all of the references refer to elderly persons and that age is always considered a pertinent demographic subset and is explicitly stated in many places in its 2005 clinical safety review guidance. In our examination of the guidance, however, we found that none of the references to elderly persons applied specifically to determining their sufficiency of representation and where sufficiency of representation is referred to, only the broader terms, such as “age” or “demographic subgroups” are used. Further, as we stated in the draft report, only about one-quarter of the medical officer clinical review summaries that we examined documented the medical officer’s review of the sufficiency of representation of elderly persons. In its comments, HHS said that FDA guidance on the clinical safety review includes a suggested table format for medical officers to use in describing the participants in the clinical drug trials. While this table suggests that the medical officers report the number of elderly persons included in the clinical drug trials, it is not a format for reporting a medical officer’s findings related to whether sufficient numbers of elderly persons were included in the clinical drug trials.


HHS commented that age references related to the review of the safety and effectiveness data clearly refer to elderly persons. While we stated in the draft report that issues pertinent to elderly persons may be discussed among reviewers, even if they are not mentioned in the written reviews, we found that analyses of safety and effectiveness for elderly persons were only documented in about two-thirds of the medical officer reviews that we examined. Moreover, while FDA developed a regulation requiring that drug sponsors report safety and effectiveness data by age, we found that drug sponsors used a variety of age categories to report these data and note that the agency has not provided guidance to its reviewers regarding their review of these data.

HHS also noted that not all of the references cited in one footnote referred to clinical drug trials specifically supporting NDAs. We agree and deleted the reference to NDAs in the footnoted sentence. Finally, HHS asserted that the adverse events associated with a nonsteroidal anti-inflammatory drug referred to in our draft report would not likely have been revealed during clinical drug trials even if more elderly persons had been studied. We deleted this example from the report.

HHS’s written comments are reprinted in enclosure IV. We incorporated technical comments as appropriate.

As arranged with your offices, unless you publicly announce the contents of this report earlier, we plan no further distribution of it until 30 days after its issue date. At that time we will send copies of this report to the Commissioner of the Food and Drug Administration and other interested parties. We will also provide copies to others upon request. In addition, the report will be available at no charge on GAO’s Web site at <http://www.gao.gov>.

If you or your staffs have any questions about this report, please contact me at (202) 512-7114 or crossem@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made major contributions to this report are listed in enclosure V.

A handwritten signature in black ink that reads "Marcia Crosse". The signature is written in a cursive style with a long horizontal line extending to the right.

Marcia Crosse
Director, Health Care

Enclosures – 5

Scope and Methodology

This report examines the Food and Drug Administration's (FDA) guidance and regulations related to (1) drug sponsors' reporting of data to describe the effects of a proposed drug on elderly persons and (2) FDA medical officers' review of safety and effectiveness data that drug sponsors provided for elderly persons.

To examine guidance and regulations on drug sponsors' reporting of data related to elderly persons, we examined FDA regulations about the study of the safety and effectiveness of drugs by age and about labeling information about the use of a drug by elderly persons. We also reviewed FDA guidance related to the study of drugs in general, the study of drugs likely to be used by elderly persons, and the format and content of a new drug application (NDA). To determine how drug sponsors have reported data related to the guidance and regulations, we reviewed all 36 NDAs submitted to FDA from January 1, 2001, through June 30, 2004, that FDA had reviewed and that were for drugs proposed to treat diseases that we determined affect elderly persons with a disproportionately greater frequency than younger persons.²⁸ For each of the 36 NDAs in our sample, we reviewed the Integrated Summary of Safety and the Integrated Summary of Efficacy that each drug sponsor included in its initial NDA submission to FDA. We determined that the data reported in the NDA summary documents were sufficiently reliable for the purposes of this report.²⁹ To determine the number of elderly participants associated with each NDA, we reviewed the overall descriptions of the clinical drug trials. To determine how drug sponsors reported safety and effectiveness data by age, we reviewed other sections of NDA summary documents that reported the relevant analyses.³⁰ We did not examine other information in the drug application.

In our review of these summary sections, we collected age of participants and other data from each NDA. Where possible, we categorized the participants from each clinical drug trial into two age categories—younger than age 65 and age 65 and older. We selected these age groups because they are identified in both FDA's guidance for drug sponsors and the preamble to the 1998 regulations.³¹ If an NDA did not report the number of clinical drug trial

²⁸Using data from the National Ambulatory Medical Care Survey (National Center for Health Statistics, National Ambulatory Medical Care Survey, 2001), we estimated the proportion of individuals 65 years and older in the population with the disease that the drug is proposed to treat. Where the indication proposed in the NDA was complex, we made our estimate using the primary condition that needs to be present. For example, if a drug is proposed to treat nausea in persons receiving chemotherapy treatment for cancer, we would select cancer as our disease of interest. We determined that these data were sufficiently reliable for the purposes of this report by reviewing relevant technical documentation, including survey methodology, weighting procedures, and code books describing the data elements used in our analyses. Based on information provided by FDA officials in April 2007 that guidance and regulations related to elderly persons in clinical drug trials had not changed since the beginning of our review, we determined that the NDAs we selected were relevant for our purposes.

²⁹We assessed the reliability of the data reported in the NDA summary documents by reviewing related documentation and interviewing agency officials knowledgeable about the data. However, we did not confirm the accuracy of the information contained in the summary documents.

³⁰A drug sponsor sometimes used different age categories to report summary information about participants, comparisons of safety by age, and comparisons of effectiveness by age.

³¹Food and Drug Administration, *Studies in Support of Special Populations: Geriatrics* (Rockville, Md.: August 1994); 63 *Fed. Reg.* 6859 (1998).

Enclosure I

participants in specific categories or even these broad age categories, we determined that we were unable to categorize the age of the participants.

To examine FDA medical officers' review of data on elderly persons, we reviewed the most recent guidance (issued in 2004 and 2005) specifically for medical officers and interviewed FDA officials responsible for overseeing the NDA review process to obtain information on how this guidance relates to the larger NDA review process. We also examined the FDA medical officer reviews completed for the 36 NDAs in our sample to obtain documentation of examinations conducted by FDA medical officers related to elderly persons. We did not observe any of the team meetings in which medical officers and others discussed the merits of each NDA.

We conducted our work from August 2004 through September 2005, in April 2006, and from April 2007 through September 2007, in accordance with generally accepted government auditing standards.

Data Provided to FDA by Drug Sponsors on Elderly Persons in Clinical Drug Trials for 36 NDAs Submitted to FDA from January 2001 through June 2004

Elderly persons were included in at least one clinical drug trial supporting each of the 36 NDAs we reviewed, though some of the trials for these NDAs excluded elderly persons on the basis of age alone.³² Drug sponsors reported summary participant data to FDA on the number of elderly persons in clinical drug trials supporting 28 of the 36 NDAs we examined. For those 28 NDAs, we could determine that 33 percent of the participants in the clinical drug trials were elderly (age 65 and older) and 65 percent were younger than age 65, according to summary information provided by drug sponsors in the NDA. Within these 28 NDAs, we were unable to determine the age of the remaining 2 percent of participants because drug sponsors did not report the age of these participants in a way that allowed us to determine how many of them were elderly. For the remaining 8 NDAs, we could not determine the number of participants that were elderly for any of the clinical drug trials because the necessary age data were not reported in the NDAs. Table 1 presents the number and percentage of clinical drug trial participants younger than age 65 and age 65 and older, and the number and percentage of those participants for whom drug sponsors did not provide adequate data to allow us to classify them into one of these two age categories.³³

³²NDAs often include data from more than one clinical drug trial.

³³Within each NDA, we included participants from those clinical drug trials for which the drug sponsor provided adequate data for us to categorize all participants as being either younger than age 65 or age 65 and older. We classified the NDAs by disease category, using the disease that the drug is proposed to treat, according to the broad categories of disease defined in the *International Classification of Diseases, Ninth Revision*. See Department of Health and Human Services, *International Classification of Diseases, Ninth Revision, Clinical Modification*, 6th ed. (Washington, D.C.: October 2003).

Table 1: Number of Persons Reported in NDA Clinical Drug Trials Categorized by Age (Younger Than Age 65 or Age 65 and Older), by Disease Category, Based on 36 NDAs Submitted to FDA from January 1, 2001, through June 30, 2004, for the Treatment of Diseases That GAO Determined Disproportionately Affected Elderly Persons

NDA, by disease category ^a	Total persons in clinical drug trials, regardless of age ^b	Persons younger than age 65		Persons age 65 and older		Persons who could not be categorized as either younger than age 65 or age 65 and older based on information in the background of NDA summary documents	
		Number	Percentage	Number	Percentage	Number	Percentage
Cancer							
1	4,493	3,649	81	844	19	0	0
2	2,881	2,347	81	534	19	0	0
3	1,468	869	59	394	27	205	14
4	1,465	0	0	0	0	1,465	100
5	1,249	708	57	541	43	0	0
6	1,052	628	60	424	40	0	0
7	936	572	61	364	39	0	0
8	928	610	66	218	23	100	11
9	426	276	65	150	35	0	0
10	361	133	37	222	61	6	2
11	256	0	0	0	0	256	100
Circulatory system							
12	9,680	3,606	37	6,074	63	0	0
13	7,105	3,357	47	3,427	48	321	5
14	4,226	1,588	38	751	18	1,887	45
15	3,626	0	0	0	0	3,626	100
16	1,025	504	49	521	51	0	0
Endocrine, nutritional, metabolic, and immunity							
17	6,016	4,108	68	1,821	30	87	1
18	5,056	4,476	89	580	11	0	0
19	2,695	2,408	89	287	11	0	0
20	1,763	1,175	67	422	24	166	9
21	612	0	0	0	0	612	100
Genitourinary system							
22	8,100	6,158	76	1,942	24	0	0
23	4,042	2,632	65	1,410	35	0	0
24	2,841	1,940	68	901	32	0	0
25	2,146	1,581	74	565	26	0	0

NDA, by disease category ^a	Total persons in clinical drug trials, regardless of age ^b	Persons younger than age 65		Persons age 65 and older		Persons who could not be categorized as either younger than age 65 or age 65 and older based on information in the background of NDA summary documents	
		Number	Percentage	Number	Percentage	Number	Percentage
		Musculoskeletal system and connective tissue					
26	14,900	10,904	73	3,996	27	0	0
27	12,911	9,028	70	3,883	30	0	0
28	8,496	0	0	0	0	8,496	100
Nervous system and sense organs							
29	2,709	646	24	2,063	76	0	0
30	1,229	684	56	485	39	60	5
31	290	0	0	0	0	290	100
Other							
32	4,870	2,788	57	2,082	43	0	0
33	3,341	2,575	77	766	23	0	0
34	2,898	0	0	0	0	2,898	100
35	954	0	0	0	0	954	100
36	774	718	93	56	7	0	0
Total	127,820	70,668	55	35,723	28	21,429	17

Source: GAO analysis of 36 NDAs submitted to FDA.

^aGAO classified the NDAs according to broad categories defined in the *International Classification of Diseases, Ninth Revision*. The “other” category combines disease categories that contained two or fewer NDAs.

^bThe total number of participants excludes 29 clinical drug trial participants from four NDAs for which the drug sponsors reported that they were missing age data.

One factor that may have limited the representation of elderly persons in some of the 36 NDAs we reviewed is that several clinical drug trials had exclusion criteria prohibiting the participation of elderly persons on the basis of their age. Clinical drug trials in 13 NDAs had exclusion criteria that prohibited the participation of at least some elderly persons on the basis of age alone; however, at least one clinical drug trial in all NDAs included some elderly participants. Specifically, 3 NDAs had at least one clinical drug trial with a criterion excluding all persons older than age 65 from participating. Drug sponsors for the other 10 NDAs had at least one clinical drug trial that used criteria excluding a subset of elderly persons—such as those older than age 70—from participating in their clinical drug trials.³⁴ FDA officials told us that drug sponsors are expected to justify any age cutoff that is used, just as they would any other decisions about their research design.

³⁴In examining only those clinical drug trials that the drug sponsors designated as most important to their NDAs, sponsors of seven of these NDAs had criteria that prohibited the participation of some older persons based on age alone.

Data Reported by Drug Sponsors to FDA on the Safety and Effectiveness of Drugs for Elderly Persons

While FDA regulations require that drug sponsors present safety and effectiveness data by age, the regulations do not define specific age subgroups to be used, thereby leaving the selection of subgroups for analysis to the drug sponsors.³⁵ For example, a drug sponsor may compare the effect of the proposed drug on the survival rate of cancer patients age 60 and older to its effect on the survival rate of those younger than age 60. According to FDA officials, instead of specifying the age categories drug sponsors must use to report data on safety and effectiveness outcomes from their clinical drug trials, the regulations FDA issued in 1998 were written broadly to allow drug sponsors flexibility to report outcome data in the manner they believe to be most appropriate. Agency officials also indicated that specific age categories, such as 65 and older, might not be appropriate for comparing safety and effectiveness data in all clinical drug trials because a clinical drug trial may have few or no participants in a specific age category. FDA officials also told us that drug sponsors know that the intent of the regulations is to encourage the examination of how elderly persons differ from younger persons in response to the drug and that the agency learns important information when an older age category—such as age 70 and older—is used.

In the 36 NDAs we reviewed, most drug sponsors used the age category of 65 and older when reporting data on a drug's safety and effectiveness by age. Specifically, drug sponsors of 30 NDAs sometimes used age 65 and older as an age category when reporting data on safety outcomes, and drug sponsors of 26 NDAs sometimes used this age category when reporting data on effectiveness outcomes.³⁶ The remaining drug sponsors either used a different age category or did not report data by age when reporting data on safety or effectiveness.³⁷

Drug sponsors are required to disclose on the drugs' labeling what they learn from clinical drug trials about the safety and effectiveness of a drug for elderly persons. Since 1998, FDA has required that drug sponsors include a Geriatric Use subsection in drug labeling that conveys the findings from the age comparisons that are reported in the NDAs and the number of elderly persons included in that drug's clinical trials, as appropriate.³⁸ The regulation provides drug sponsors with a choice of three primary statements to be used in the Geriatric Use subsection. First, if there have not been sufficient numbers of elderly participants in clinical drug trials to determine whether those age 65 and over respond differently to the drug, it should be noted in the labeling along with a statement that dose selection for an elderly patient proceed with caution, generally starting at the low end of the dosing range.

³⁵See 21 C.F.R. § 314.50(d)(5)(v), (vi)(a); § 312.33(a)(2) (2007).

³⁶A drug sponsor sometimes used different age categories to report summary information about participants, comparisons of safety by age, and comparisons of effectiveness by age.

³⁷Three NDAs did not include any effectiveness data by age and one of these NDAs also did not report any safety data by age. With regard to the one NDA without any safety or effectiveness data by age, the drug did not perform successfully, and FDA did not approve the NDA. FDA officials told us that, for the remaining two NDAs, such presentations were either unnecessary or not possible. For one of these two, FDA officials stated that it was not necessary for the drug sponsor to report effectiveness data by age because all of the clinical drug trial participants were between the ages of 55 and 80. For the remaining NDA, FDA officials told us that because the drug sponsors studied elderly persons and younger adults in separate clinical drug trials, the drug sponsors could not provide such comparisons.

³⁸62 *Fed. Reg.* 45313, 45325 (Aug. 27, 1997) (codified at 21 C.F.R. § 201.57(c)(9)(v) (2007)).

Enclosure III

Second, if there have been sufficient numbers of elderly participants in clinical drug trials to make it likely that differences in safety and effectiveness between older and younger participants would have been detected, but no such differences were found, it should be noted in the labeling. The labeling should also note the percentage or total number of trial participants who were 65 years of age and older and 75 years of age and older. Third, if there is evidence that there are differences in safety or effectiveness between elderly and younger participants or that elderly persons require dosage adjustments or monitoring, it should be noted in the labeling along with a description of these differences.

In addition to the three statements provided by FDA, the regulation also allows drug sponsors to suggest alternative statements that FDA may approve if it determines them to be accurate and appropriate. Further, FDA may permit omission of a Geriatric Use statement if the agency determines that none of the statements are appropriate or relevant to a drug's labeling. Of the 21 drug labels that had been approved through June 2004, from our sample of 36 NDAs, we found that 15 used one of the types of labeling statements above, while 5 used alternative statements approved by FDA. One drug label omitted the Geriatric Use subsection.

Comments from the Department of Health and Human Services



DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Assistant Secretary
for Legislation

Washington, D.C. 20201

SEP 11 2007

Marcia Crosse
Director, Health Care
U.S. Government Accountability Office
Washington, DC 20548

Dear Ms. Crosse:

Enclosed are the Department's comments on U.S. Government Accountability Office's (GAO) report entitled: "Prescription Drugs: FDA Guidance and Regulations Related to Data on Elderly Persons in Clinical Drug Trials" GAO 07-47R.

The department appreciates the opportunity to review and comment on this report before its publication.

Sincerely,

R. Hemard

Vincent J. Ventimiglia

for Assistant Secretary for Legislation

COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES ON THE U.S. GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT ENTITLED: "FDA GUIDANCE AND REGULATIONS RELATED TO DATA ON ELDERLY PERSONS IN CLINICAL DRUG TRIALS"(GAO-07-47R)

1. Overall the report acknowledges FDA's extensive efforts to assure reasonable representation of the elderly in clinical trials and mentions many guidances, but there is no place in the report where FDA's long-standing (beginning in 1982) and extensive efforts in this area are clearly and completely summarized. Such a summary would convey the scope of FDA's efforts in this regard. It would include FDA's Guideline for the Study of Drugs Likely to be Used in the Elderly; the ICH Guidance on the same issue (E7: Studies in Support of Special Populations: Geriatrics); the extensive emphasis on demographic data in the 1988 Guideline for the Format and Content of the Clinical and Statistical Sections of an Application; the 1998 rule requiring demographic analysis (21 CFR 314.50(d)(v)(vi)); and the emphasis on demographic analyses in the 2005 Reviewer Guidance: Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review, and in the review template used by clinical reviewers on demographic subgroups, specifically including the elderly. This summary would be helpful because these cumulative efforts show clearly that study of the elderly has been a matter of great importance to FDA for almost 2 decades.

The principal criticism in the report is that FDA does not adequately convey to its reviewers the agency's expectations with regard to the need to review safety and effectiveness data related to elderly persons, apparently because in identifying age as a demographic characteristic of interest, FDA does not specifically identify the elderly as an age group of particular interest. As the report points out, FDA disagrees with this conclusion. The agency specifically asks reviewers to conduct demographic analyses by gender, race, and age; the only reason for conducting these analyses is to look for differences in effectiveness and safety in men versus women, blacks versus whites, and old versus young, and in the last case the interest is almost always primarily whether older people respond less well or have more adverse effects. This interest is recognized by every reviewer and it is not necessary to state repeatedly that our interest is in the elderly. Moreover, there are in fact numerous explicit references in the documents cited above to comparing safety and effectiveness in old and young. Some of these references are listed in the comments below.

2. The draft report states on page 5 that "agency guidance does not direct medical officers to report whether sufficient numbers of elderly persons participated in NDA clinical drug trials." Similar language is found on page 12.

a. In fact, the Clinical Review Template asks reviewers to consider:

i. Whether efficacy findings are limited by "limitations of the population studied";

COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES ON THE U.S. GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT ENTITLED: "FDA GUIDANCE AND REGULATIONS RELATED TO DATA ON ELDERLY PERSONS IN CLINICAL DRUG TRIALS"(GAO-07-47R)

- ii. Adequacy of the assessment in special populations (which always includes the elderly);
- iii. Adequacy of patient exposure in terms of "appropriate demographic subsets of patients" (see section 7.2);
- iv. Whether "adequate numbers of subjects were exposed, including adequate numbers of various demographic subjects" and "whether patients excluded from the study (e.g., diabetes, people over 75. . .) limit the relevance of safety assessments";
- v. "Explorations for drug-demographic interactions";
- vi. "Special dosing instructions based on demographics: race, gender, age for adults".

b. The Safety Review Guidance emphasizes demographic subgroups repeatedly, e.g. in analyses of deaths (page 14), adverse drop-outs (page 18), common adverse effects (page 24), laboratory abnormalities (page 29). Age is always considered to be a demographic subgroup, even if not explicitly stated as such.

c. The FDA guidance on the Clinical Safety Review (page 36) specifically calls for showing the numbers of patients by age, gender, and race and, in table 7.2.1.2.1 specifically shows an age ≥ 65 row. On page 38 the reviewer is specifically asked to address "whether an adequate number of subjects were exposed to the drug, including adequate numbers of various demographic subsets." Again, although GAO is technically correct that the guidance does not specifically reference on all occasions that age as a demographic subset, the fact that age is always considered as a pertinent demographic subset is entirely obvious to reviewers and is explicitly stated in many places.

3. On page 12, the draft report states that "FDA expectations that medical officers review safety and effectiveness data related to elderly persons are not conveyed in agency guidance," apparently because our guidance refers to age broadly, not specifically to elderly or "people over 65." The draft asserts that FDA is more specific in its references to other demographic subgroups. This is incorrect. While "age" in the abstract could mean 10-20, 20-30, 40-50, etc, it is wholly clear from the content (described above) of the Clinical Safety Review guidance, and from FDA's two guidance documents on studies of drugs in the elderly ("Guideline for the Study of Drugs Likely to be Used in the Elderly" (1989); ICH E7: Studies in Support of Special Populations: Geriatrics (1994)), as well as from the fact that the physician package insert includes a specific section on geriatrics, that references to "age" are, implicitly, references to the elderly.

COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES ON THE U.S. GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT ENTITLED: "FDA GUIDANCE AND REGULATIONS RELATED TO DATA ON ELDERLY PERSONS IN CLINICAL DRUG TRIALS"(GAO-07-47R)

The draft report notes (page 13) that FDA told GAO that reviewers all know that "age" and "demographic analyses" mean elderly, but the draft report then goes on to suggest that this understanding may not be complete across all medical officers. In fact, interest in "age" can have no other meaning. If the interest were in pediatric use, that terminology would be used; thus, references to analysis by age implicitly refer to the elderly. And, as noted, this interest has been signaled repeatedly.

4. On page 13, the draft report says that medical officers are not asked to "determine whether sufficient numbers of elderly persons participated in NDA clinical drug trials." As the quote from page 38 of the Clinical Safety Review guidance above makes clear, they are in fact asked that very thing.

SPECIFIC GENERAL COMMENTS

1. p 3: Footnote 6 is to support the contention that there is concern about inclusion of elderly persons in clinical drug trials supporting NDAs. That concern has certainly been expressed but note that the Lee, et al reference does not refer to trials supporting NDAs but rather to trials of acute coronary syndromes generally. We are not sure what the Mitchell reference refers to, and therefore suggest that GAO confirm that it pertains to trials supporting NDAs. Talarico, et al concluded that the elderly were under-represented compared to disease prevalence, but that does not necessarily mean there were not sufficient elderly patients for analysis. No one has argued that clinical trials must contain age representation proportional to demographic prevalence; what is necessary is to include sufficient numbers of elderly to provide sufficient exposure (something that is admittedly a judgment call). Talarico, et al do not address that issue, although they certainly raise the concern, especially for the very old, that representation might be inadequate and that responses could well differ by age.

2. p 8: Footnote 13 presumably refers to Oralflex (benoxapofen). It is not likely that the rare late-developing serious liver injury that led to withdrawal of the drug was common enough to have shown up in clinical trials; thus, the fact that the trials did not include extensive numbers of elderly persons in all likelihood did not affect the situation with regard to the adverse event at issue.

Enclosure V

GAO Contact and Staff Acknowledgments

GAO Contact

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Acknowledgments

In addition to the contact named above, Thomas Conahan, Assistant Director; George Bogart; William Hadley; Cathy Hamann; Carolyn Feis Korman; and Gloria Taylor made key contributions to this report.

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