Guidance for Industry

Self-Selection Studies for Nonprescription Drug Products

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
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Guidance for Industry[1] Self-Selection Studies for Nonprescription Drug Products

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I. INTRODUCTION

This guidance is intended to provide recommendations to industry involved in developing and conducting self-selection studies to support an application for nonprescription drug products. A self-selection study assesses the ability of consumers to apply drug labeling information to their personal health situation to make correct decisions about whether or not it is appropriate for them to use a drug product.

This guidance covers general principles related to the conduct of self-selection studies, including study design, methodology, and analyses, and should not be considered a substitute for an FDA review of specific protocols. This guidance also incorporates advice obtained from the Nonprescription Drugs Advisory Committee at a meeting on September 25, 2006, at which the committee considered issues related to analysis and interpretation of consumer studies conducted to support marketing of nonprescription drug products.[2]

FDA's guidance documents, including this guidance, 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 the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by the Division of Nonprescription Clinical Evaluation and the Office of Biostatistics in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] The transcript from the September 25, 2006, Nonprescription Drugs Advisory Committee meeting is available at http://www.fda.gov/ohrms/dockets/ac/06/transcripts/2006-4230t.pdf.

II. BACKGROUND

The development of certain nonprescription drug products may include conducting consumer studies, in addition to the required safety and efficacy studies. The consumer study process may include label comprehension studies, which assess consumer understanding of major communication elements,[3] and self-selection studies, which test whether consumers can apply the label information to their personal medical situations and make correct decisions to use or not use the drug product (self-selection decision). We recommend conducting a label comprehension study before conducting a self-selection study.

If label comprehension studies demonstrate that major communication elements on the label are well understood, a self-selection study may be needed to test whether consumers can make appropriate self-selection decisions based on the information contained in the label.

Some of the circumstances under which we might recommend a self-selection study include:

- The drug product is for a new nonprescription indication
- The drug product is for a new nonprescription target population
- There are specific populations who should not use the proposed nonprescription drug product (e.g., diabetics, transplant recipients)
- A substantive labeling change has been proposed for an approved nonprescription drug product that may affect the appropriate nonprescription population (e.g., a change in the warnings, directions for use)

We encourage sponsors to seek FDA consultation and advice on a protocol for a self-selection study.

If information on how consumers will use the drug product is needed, an actual use study can be conducted. Actual use studies are outside the scope of this guidance.

III. STUDY DESIGN AND CONDUCT

In general, self-selection studies can be open-label, uncontrolled trials. The following are general recommendations for the design and conduct of a self-selection study. Subsequent sections provide a more detailed discussion of each recommendation.

- State the purpose and objectives of the study

[3] See the guidance for industry *Label Comprehension Studies for Nonprescription Products*. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

- Specify a study design that meets the study objectives and calculate the appropriate sample size

- Enroll a population appropriate for the study objectives

- Enroll subjects with low and normal literacy skills

- When necessary, enrich the study with subjects who have relative or absolute contraindications to use of the drug product

- Use labeling that is as similar as possible to the final drug product label

- Construct a questionnaire that targets the study objectives

- Minimize factors that may contribute to a biased study (e.g., sampling, recruitment strategies, leading questions, interviews that bias the responses in a particular direction)

- Consider pilot testing before conducting a large self-selection study

A. Study Objectives

1. Primary Objective

In general, the primary objective(s) of a self-selection study should be to assess if subjects, after reading the drug product label, can make a correct self-selection decision(s) based on their medical history.

2. Secondary Objectives

Secondary objectives may be to assess the reasons why subjects make incorrect self-selection decisions. The data come from questions asked to elicit reasons for incorrect self-selection. It is important to determine why subjects make incorrect decisions to better understand what label revisions may need to be made to improve correct self-selection.

B. Study Population

The study population should be defined based on the study objectives. Some studies may include any subject who may have an interest in using the drug product, regardless of age, sex, underlying medical conditions, and use of concomitant medications. Other studies may target a particular population of interest (e.g., subjects with a specific disease for whom use of the drug product may be contraindicated). Because nonprescription drug products are available for purchase without the input of a health care professional and no drug product is administered in the study, exclusion criteria should be minimal (e.g., inability to speak, read, and understand English).

Self-selection studies should also enroll an adequate number of subjects who have low literacy skills to examine the ability of this subgroup to make a correct self-selection decision. The proportion of low literacy subjects in a study sample should be representative of the proportion of adults in the United States with basic literacy skills, based on available national data. Education level is not a reliable substitute for literacy testing. At screening, the sponsor should assess literacy levels of the study subjects by administering a validated instrument such as the Rapid Estimate of Adult Literacy in Medicine (REALM) test,[4] REALM-Teen for testing adolescents[5] or the Test of Functional Health Literacy in Adults (TOFHLA or S-TOFHLA).[6,7,8] Investigators should receive training to properly administer literacy tests.

C. Statistical Considerations and Data Analysis

1. Primary Endpoints, Success Criteria, and Mitigating Factors

The primary endpoint for a self-selection study should be the proportion of the study subjects who make a correct self-selection decision. A correct self-selection decision is based on the label element(s) that are needed to make an appropriate decision whether or not to use a drug product (self-selection decision). A correct self-selection decision can be based on a single label element or a composite of several label elements depending on the drug product.

For example, the drug product may have only one contraindication: diabetics should not use the drug product. In this case, a correct self-selection decision for a diabetic (regardless as to whether he or she has the condition for which the drug product is indicated) would be that the drug product is not appropriate for his or her use. In contrast, an incorrect self-selection decision would be a diabetic who selects to use the drug product. An example of a composite of several label elements would be a drug product that is only for women between 18 and 65 years of age who do not have heart disease or hypertension. A correct self-selection decision would be a woman between 18 and 65 years of age who has the labeled indication and does not have heart disease or hypertension who selects to use the drug product. An incorrect self-selection decision would be a 55-year-old woman with hypertension who selects to use the drug product (whether or not she has the indication).

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[4] REALM: Davis, TC et al., 1993, Rapid Estimate of Adult Literacy in Medicine: A Shortened Screening Instrument, *Family Medicine*, 25:391-395.

[5] REALM-Teen: Davis, TC et al., 2006, Development and Validation of the Rapid Estimate of Adolescent Literacy in Medicine (REALM-Teen); A Tool to Screen Adolescents for Below-Grade Reading in Health Care Settings, *Pediatrics*, 118 (6): e1707-1714.

[6] TOFHLA: Parker, RM et al., 1995, The Test of Functional Health Literacy in Adults: A New Instrument for Measuring Patients' Literacy Skills, *Journal of General Internal Medicine*, 10:537-541.

[7] Baker, DW et al., 1999, Development of a Brief Test to Measure Functional Health Literacy, *Patient Education and Counseling*, 38:33-42.

[8] The REALM and TOFHLA were designed as rapid screening tools that were validated against the Wide Range Achievement Test for literacy. Therefore, use of these instruments to screen literacy levels within the context of health is appropriate.

Success criteria should be related to the predefined target level for correct self-selection. This target level should be justified based upon a clinical rationale. Success criteria should be defined using the confidence interval approach: the study can be claimed as a success only when the lower limit of a predefined two-sided 95 percent (or one-sided 97.5 percent) confidence interval for the correct self-selection rate is above the target level. We recommend using a two-sided 95 percent confidence interval to estimate the correct self-selection rate as well as to define the success criteria. This approach allows consideration of variability within the study data and sets the type I error rate for one-sided tests (2.5 percent) at half the conventional type I error rate (5 percent) used in two-sided tests.

Reasonable predefined mitigating factors may be acceptable in certain circumstances. Mitigating factors are subject responses that would allow what appears to be an incorrect self-selection decision to be considered a correct self-selection decision. The following is an example of a mitigating factor: subjects who make an incorrect self-selection decision based on age, but who are within 1 year of the labeled age and verbalize an understanding of the correct age. For example, a subject who is 54 makes an incorrect self-selection decision based on age for a drug product that is labeled for adults 55 and older. After being asked a nonleading, open-ended question to elicit more information about his or her decision, the subject states that he or she knows the drug product is labeled for people aged 55 or older, but because he or she will be 55 within a month he or she feels it is okay to take the drug product.

The definition of a correct self-selection decision, mitigating factors, and the target success criteria for correct self-selection should be determined in advance of study enrollment and specified in the study protocol. With more complicated labels, such as those with multiple decision points, we recognize that not every subject will be 100 percent correct based on all the label elements required to make a self-selection decision and that some label elements have greater clinical significance than others if not heeded. Therefore, we recommend that sponsors discuss with the FDA the label elements to be used to define correct self-selection, the mitigating factors, and the predetermined success criteria before conducting the study.

2. Sample Size Considerations

The number of subjects in a self-selection study should be large enough to provide a reliable answer to the primary objective. Sizing of such a study should be based on the success criteria. This generally involves the predefined target level for correct self-selection, the assumed percent of correct self-selection for the study population, the type I error rate, and the type II error rate (or the study power).

The type I error rate should be set at 2.5 percent. The type II error rate generally should be in the range of 10 percent to 20 percent; in certain circumstances, it may be appropriate to set the type II error rate lower than 10 percent. Target levels for correct self-selection can vary depending upon the medical significance of incorrect self-selection.

The number of subjects in a self-selection study should be large enough to evaluate the primary endpoint for important subgroups, such as the low literate subgroup or any other subgroup of

interest. Alternatively, a targeted self-selection study can be conducted to assess a specific subgroup.

3. Data Analysis

The principal features of the planned analysis should be defined in the protocol. The statistical methods and the analysis of the primary and secondary endpoints also should be specified in the protocol. Methods for constructing a two-sided 95 percent confidence interval to estimate and define the success criteria for the correct self-selection rate should be described, including a detailed description of the numerators and denominators. Methods for handling missing data should be specified.

Typically, a comprehensive statistical analysis plan should be included in the protocol and address all the details of the data analysis. In cases where the comprehensive statistical analysis plan is prepared as a separate document, it should be prepared before the results of the study are known and it should be submitted for FDA review.

D. Questionnaire Design

A questionnaire is typically used to collect data in a self-selection study. The questionnaire design should: (1) reflect the study objectives; and (2) optimize the validity and interpretability of the information collected. Wording, question structure, and question sequences can significantly affect the validity and interpretability of the data collected. A detailed discussion of questionnaire development is beyond the scope of this guidance. However, the following points merit particular consideration.

1. Questions That Address the Study Objectives

The following are general recommendations about the types of questions that address the study objectives.

- The self-selection question: The first question asked should be an open-ended self-selection question (e.g., "Is it okay for you to use this medication?") followed by a nonleading probing question (e.g., "Why do you feel it is okay for you to use the medication?" or "Why do you feel it is not okay for you to use the medication?").

- Open-ended questions: Open-ended questions that follow the self-selection question may help provide additional data for the analysis. Additional questions used to elicit more information should be nonleading and be used sparingly so as not to prompt the subject to provide a desired response. An example of a nonleading question for subjects who say that it is "okay for them to use the medication," would be to then ask "Why do you say that?" This question enables multiple possible responses including "after I talked to my doctor." By contrast, an example of a leading question, where the correct response is that a subject should talk to his or her doctor before using the drug product, would be to ask "is there anything you would do before you start using the medication?" This question may direct subjects toward a correct answer. Additionally, subjects who feel obligated to

provide an answer may respond with "talk to my doctor" as a logical default answer, which may introduce bias.

- Medical history questions: Medical history questions should be asked after the self-selection question to prevent bias that can occur from informing the subject to focus on specific label elements. The medical history questions should be asked in consumer-friendly language and be based on obtaining health information related to the drug product's indications, warnings, and contraindications.

- Additional open-ended questions: Additional open-ended questions should be asked to assess reasons why subjects make incorrect self-selection decisions. It is important to determine why subjects make incorrect decisions to better understand what label revisions may need to be made to improve correct self-selection. As noted above, answers to these open-ended questions may also be found to mitigate an incorrect self-selection decision under certain circumstances. Answers that may be used to mitigate an incorrect self-selection decision should be determined before the study begins and should be included in the protocol.

Sponsors sometimes choose to add a question asking subjects whether or not they would purchase the drug product. We do not consider purchase decision data to have any bearing on the interpretation of self-selection data or study outcomes. These questions should be asked only following the completion of the self-selection portion of the assessment. The response to a purchase decision question should not be used to mitigate a self-selection decision (e.g., subjects who incorrectly make a self-selection decision, but choose not to purchase the drug product should not be considered correct in their self-selection decision). Because a purchase decision is generally influenced by cost, we consider it to be an unreliable surrogate for a self-selection decision.

2. General Questionnaire Design Concepts

The following are general recommendations about the design of questionnaires.

- Simple vocabulary should be used, and questions should be pretested to ensure the questions elicit the intended information.

- Questions should be direct, specific, and unambiguous. Each question should address a single item or issue.

- Questions should be ordered so that information contained in a question does not bias a subject's ability to answer subsequent questions.

- Response choices in multiple-choice questions should be independent and contain only one correct answer.

- When listing response categories for multiple-choice questions (e.g., to assess the medical history), *I don't know* should be included as one of the response categories to

give subjects permission to admit that they do not know so they avoid guessing. The category *other* should also be included to allow subjects to add something that may not be listed as a choice.

- Questions intended to measure the behavioral intent of the subject should not be used. Testing behavior is outside the scope of a self-selection study. If information about how subjects would behave under real-world conditions is needed, an actual use study should be conducted.

The questionnaire can be pretested with a sample of respondents similar to the target population to ascertain that the questionnaire is eliciting the intended information.

E. Study Conduct and Location

Advertisements for the study should not contain any information about the proposed drug product. If there is initial telephone contact, subjects should receive only information on how and where to participate in the study. The study site can be in a mall, or in other places frequented by consumers. It also can be designed to simulate an actual purchase site. Occasionally, it may be necessary to use a clinical setting so a specific population can be accessed. Also, a clinical setting may be appropriate in situations where lab tests are needed to verify correct self-selection decision. The study setting should be comfortable and well lit for reading. Subjects should have adequate time to read the label and be able to refer to it throughout the testing period. However, subjects should not be prompted to refer to the label during testing.

Subjects should receive sufficient instruction on the format and conduct of the study and the expected length of time it will take to participate. Two general approaches to administering the questionnaire that can be considered include self-administration or asking the questions using a trained interviewer. Using a trained interviewer may lessen the chance that low literate subjects will incorrectly respond because they cannot comprehend the written question when, in fact, they comprehend the label. Using an interviewer, however, may lead to interviewer bias particularly if the interviewer leads the subject to elicit a response. Interviewers involved in the study should be adequately trained and have established protocols and/or scripts to adhere to, especially regarding questions that subjects might ask. Inherent bias can occur with any data collection method. Therefore, sponsors should provide a rationale for why a particular method was chosen and should address any potential bias.

F. Data Collection and Recording

Verbatim responses to all open-ended questions should be recorded. The procedure for coding, categorizing, and analyzing verbatim responses to open-ended questions should be specified in advance and described in the protocol. In addition, all correct and incorrect answers to closed-ended questions should be prespecified. Any post-hoc coding for open-ended questions should be documented.

Methods for verification of complete and accurate recording of study data should be described in the protocol or the statistical analysis plan (i.e., subjects' responses, data entry, missing data, and data coding).

IV. FINAL REPORT

The final report should summarize the study design, study conduct, and interpretation of the study results. The demographic characteristics of the study subjects, including literacy level, should be presented.

The final report should assess whether the appropriate population has been enrolled to adequately assess self-selection decision making. The final report should describe the nature of the recruitment effort and the response rate (i.e., the proportion of screened subjects who were actually enrolled in the study). If possible, potential subjects who were excluded, or who chose not to enroll in the study, should be characterized by demographic factors and the reasons for nonparticipation. Enrolled subjects should be characterized as to relevant demographic factors and whether or not they completed the entire study. Reasons why subjects failed to complete the study should be provided in the final report.

The presentation of the study results should include both the overall correct self-selection rates and correct self-selection rates in appropriate subsets (e.g., literacy level, sex, age, race, and presence of high risk factors).

The acceptable success criteria for correct self-selection should be based on meeting the success criteria that were established before the study began and were documented in the protocol and/or the statistical analysis plan. The interpretation of the quantitative data should be augmented by the verbatim responses collected from open-ended, nonleading questions used to assess the self-selection. Thus, an analysis of both quantitative and qualitative data types should be provided to support and interpret the study findings.