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November 15, 2011

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2011-D-0620-0001

Dear Sir or Madam,

Enclosed herein are comments on "Guidance for Industry; Self-Selection Studies for Nonprescription Drug Products, published as *Draft Guidance*¹. The Consumer Healthcare Products Association (CHPA) is the national trade association representing the leading manufacturers and distributors of OTC medicines and dietary supplements in the United States. CHPA and its member companies have an interest and expertise in self-selection studies and support FDA's efforts to develop guidance for industry on this important topic. Self-selection studies are an important tool to assess consumer understanding and application of information on labels of nonprescription drug products and the decisions made based on this information.

CHPA's comments on the Draft Guidance are organized into General Comments and Detailed Comments by Section (Attachment 1).

1. General Comments

- a. CHPA agrees that FDA guidance is appropriate for self-selection studies. There is no one template that can be applied to all studies. Many aspects of design are highly dependent on the individual application and the individual drug candidate. The science and methodology used in self-selection studies should be recognized as unique vs. other related fields, such as clinical trial and behavioral research. This science continues to evolve and attempts to force-fit standards from clinical trial research should be discouraged. We suggest FDA incorporate these points into the document.
- b. As written, the Draft Guidance is very general and vague, and it contains very few examples to illustrate the points made. CHPA encourages FDA to include more examples throughout the document.

CHPA and its members look forward to working with FDA to further develop this guidance. Please contact me if you have any questions about our submission.

Respectfully submitted,

A handwritten signature in black ink that reads "Barbara A. Kochanowski". The signature is written in a cursive style.

Barbara A. Kochanowski, Ph.D.
Vice President, Regulatory & Scientific Affairs

¹ **Federal Register**, Vol. 76, No. 181, p 58018, September 19, 2011.

Attachment 1
CHPA Detailed Comments on Draft Guidance for Industry on Self-Selection (SS) Studies for Nonprescription Drug Products

Line Numbers	Section Title
III.	Study Design and Conduct
General	<p>CHPA recommends FDA acknowledge that self-selection studies can be stand-alone studies, or may be tagged on to a label comprehension study or to an actual use study, as stated by FDA previously²³. In this case, relevant guidance for self-selection studies would still apply.</p> <p>CHPA recommends FDA acknowledge “targeted self-selection studies” (e.g. to focus on one or several key label elements) are also conducted, and ensure that the guidance allow for these studies.</p>
89-90	The draft guidance discusses enriching samples with populations of special interest. It would be helpful to provide examples of when enrichment might be necessary. Guidance is also needed on how such enrichments are to be handled in statistical analysis, since the inclusion of an enriched sample will render the aggregate sample unrepresentative. If the outcome is to be evaluated on the entire sample, weighting the sample to account for enrichment may be appropriate. If the outcome is to be evaluated separately on the enrichment sample, then issues regarding sample size for such samples arise. Further, the performance of the enrichment sample will almost always be most relevant to a particular label element (e.g., avoidance of use by those with a particular medical condition), so guidance is needed on what end-points are relevant to assess in the enrichment samples.
A.2	Does FDA have a process by which to establish secondary objectives? It would be helpful to provide examples of secondary objectives, e.g. overall results in subpopulations.
B 127-135	CHPA agrees that self-selection studies should include a sampling of low-literate consumers in numbers proportional to their representation in the population. However, by stating in line 130 that this proportion be based on national data, FDA are implying that National Assessment of Adult Literacy (NAAL) data be used to determine this proportion. As far as we are aware, this is the only national database on this topic. CHPA has significant concerns with using these data, the utmost being that the survey instrument is not publically available. Hence, it has not been possible to conduct independent research to verify the results. CHPA recommends the guidance allow for alternatives to this approach. For example, by administering tests such as the REALM to a representative sample of adults, one would find approximately 15-20% of the adult population designated “low medical/health literate”, as opposed to approximately 30% by using the NAAL data. This sampling approach should be acceptable for self-selection studies. This topic of selecting an appropriate low literate population is one that deserves more dialogue between FDA and stakeholders before establishing guidance.
C	Are statistics expected on secondary objectives? If so, guidance should be included. This section excludes any mention of having the appropriate indication (only mentions contraindications). It would be helpful to include some discussion on the appropriate indication.

² The transcript from the September 25, 2006, Nonprescription Drugs Advisory Committee meeting at <http://www.fda.gov/ohrms/dockets/ac/06/transcripts/2006-4230t.pdf>, p23.

³ Guidance for Industry: Label Comprehension Studies for Nonprescription Drug Products, August 2010, at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM143834.pdf>

C.1	<p>CHPA has previously filed detailed comments to FDA regarding statistical considerations for label comprehension studies. Much of that discussion applies to self-selection studies as well. We agree that success criteria should be defined using the confidence interval approach. We disagree with FDA's recommendation of using a two-sided 95 percent confidence interval to estimate the correct self-selection rate as well as to define the success criteria. A two-sided 95% confidence interval represents an extremely conservative and unnecessary step. It is most commonly appropriate to use a one-sided test at the 5% level (lower 95% confidence limit) in the general sample. A type I error rate of 5% is reasonable and based on precedent. Bioequivalence, for example, is typically established using two one-sided tests, each at the 5% level and is often implemented as a two-sided 90% confidence interval. FDA's approach continues to appear to derive from traditional clinical research. CHPA recommends additional dialogue with industry and outside experts to reach a reasonable approach to statistical analysis for self-selection studies.</p>
141-157 182-187	<p>In the earlier reference (141-157), the draft guidance appears to imply that sponsors should define a single self-selection end-point that encompasses all self-selection elements on the label. This could have undesirable consequences. First, it would give equal weight to all self-selection elements, without regard to their clinical consequences. This would be contrary to the discussion at the FDA Advisory Committee meeting in September 2006 (see footnote 2), to the principles articulated in FDA's Guidance for label comprehension studies, and to the approach articulated in the Brass et al. (2009)⁴ article. A further undesirable consequence of including all self-selection elements in the evaluation is that the probability of success is strongly related to the number of self-selection elements, just by chance alone, without regard to the clinical importance of the self-selection decisions.</p> <p>Consistent with the latter reference (182-187), we believe that the primary end-points defined for self-selection studies should be limited to those self-selection elements associated with significant clinical risks, with self-selection on other elements being treated as secondary end-points. As specified by the FDA guidance on label comprehension studies (see footnote 3), designation of self-selection elements as primary or secondary end-points would be subject to discussion and agreement between FDA and the sponsor. The guidance for self-selection studies should identify mechanisms and expectations for acceptable scoring, including statistical analysis, associated with varied outcomes across multiple endpoints.</p>
185-187	<p>We recommend this language be modified to read: Therefore, we recommend that sponsors discuss with the FDA the label elements to be used to define correct self-selection [<i>including the possibility of using multiple self-selection outcomes rather than a single composite</i>], the mitigating factors, and the predetermined success criteria before conducting the study.</p>
C.2 202-204	<p>It would be helpful to provide more clarity regarding "large enough". The draft guidance implies that self-selection performance should be evaluated separately in important sub-groups, e.g. low literate. If the sample size of the entire self-selection population is adequate to statistically evaluate self-selection outcomes, then the sample size of low literacy subjects will be inadequate for statistical evaluation. We suggest self-selection endpoints should be evaluated in the sample as a whole, with adequate representation of low literacy persons as part of the larger sample and evaluation.</p>

⁴ Brass EP, Shay LE, Leonard-Segal A. Analysis of end points in consumer research in support of switching drugs from prescription to over-the-counter status: The concept of end-point hierarchies. Clin Pharmacol Therapeut 2009, 85: 369-374.

D.	<p>It would be helpful if FDA would provide some general guidance on question types/formats that are potentially acceptable and likely unacceptable (e.g. true/false) and state that FDA is willing to review questions, at the sponsor's request, and approve the exact wording and question format in advance.</p> <p>We recommend FDA state that the wording for critical endpoints be agreed between FDA and the sponsor.</p>
D.1 235-238	<p>Many labels contain conditional contraindications directing consumers to ask a doctor before using the medication. The draft guidance should address how such label elements are to be assessed in self-selection studies.</p>
246-249	<p><i>Open-ended (leading) questions:</i> The draft guidance provides recommendations of leading vs. non-leading questions. For example, "Is there anything you would do before you start using the medication?" is leading, since it may direct subjects toward a correct answer. CHPA notes that while asking as such may be leading, rephrasing the question as "What, if anything, would you do...", since this does not direct subjects toward a correct answer. We suggest this example also be included in the document.</p>
253-257	<p><i>Medical history questions:</i> The draft guidance currently states that medical history questions should be asked after the self-selection questions to prevent bias. In some cases (e.g., to target users with a certain condition), it may be important to screen for medical conditions in a masked manner, up front, before the self-selection study questions are asked. The guidance should allow for these situations.</p>
259-266	<p><i>Additional open-ended questions:</i> The draft guidance implies that all possible mitigating responses can and should be identified <i>a priori</i>. This is not possible. If important information on mitigating responses is identified as part of the study, this information should be included in the study report and considered in the interpretation of study results, assuming it is medically valid. The guidance should allow sufficient flexibility for subjects to state unexpected responses.</p>
268-276	<p>The draft guidance states that FDA does not consider purchase decision data to have any bearing on the interpretation of self-selection data or study outcomes. CHPA disagrees. There are many examples of self-selection studies where purchase data provide valuable understanding of how a consumer reads the label. FDA also states that a purchase decision is generally influenced by cost. CHPA disagrees. A purchase decision may or not be influenced by cost. Taken together, a self-selection question and a purchase decision question, and the reasons for the answers, provide valuable insight into what consumers are thinking. Thus, asking both questions is consistent with FDA's goal of understanding reasons for consumer behavior. The guidance should state that both questions may be appropriate. This point of view is consistent with advice FDA received from its experts in 2006.⁵</p>
294-298	<p>FDA should recommend how "I don't know" responses should be handled for open-ended questions.</p>
E	<p><i>Study Conduct and Location:</i></p> <p>Advertisements: Since self-selection studies are conducted among persons interested in the test product, to attract such populations, the advertisements must state something about the product (at a minimum, the intended indications) or a medical condition. The guidance should allow for this.</p>

⁵ The transcript from the September 25, 2006, Nonprescription Drugs Advisory Committee meeting at <http://www.fda.gov.gov/ohrms/dockets/ac/06/transcripts/2006-4230t.pdf>, p209-325.

315-316	It would be helpful to clarify or provide some examples of where lab tests may be needed to verify a correct self-selection decision. Additionally, a separate section of the guidance should be added to discuss verification or validation. These are important concepts and are not addressed in the draft guidance.
318-319	CHPA agrees that subjects should not be repeatedly prompted to refer to the product label during testing. However, the guidance should be clarified to state that subjects should be informed at the study start that they should refer to the product label as needed during the test period.
IV.	Final Report
General	Recommend stating if submission of a full data set is expected by FDA and if so, providing recommendations for the format of the data.
355-359	The meaning of the intent of the sentence beginning with “if possible” is not clear. If a potential subject didn’t respond or agree to participate, it is not normally possible to obtain additional information (demographic factors, reasons for not participating).
367-370	CHPA agrees that an analysis of both quantitative and qualitative data types should be provided in the final report. We recommend eliminating any references to how one data type augments or supports the other, as this may vary from study to study.