Comments and Suggestions on Draft Guidance:

Self-Selection Studies for Nonprescription Drug Products (Docket No. FDA-2011-D-0620)

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INTRODUCTION

On September 19, 2011 the Center for Drug Evaluation and Research (CDER) announced a draft guidance for industry titled *Self-Selection Studies for Non-Prescription Drug Products* (Docket No. FDA-2011-D-0620, 9369dft.doc) and invited public comment. This document is a response from PEGUS Research, Inc. containing comments and suggestions on the draft guidance.

COMMENTS AND SUGGESTIONS

The table below identifies specific elements from the draft guidance by line number, and presents our comments and suggestions for each.

Line #(s): Guidance Document Text / Comments:

89-90 *"When necessary, enrich the study with subjects who have…contraindications to use of the drug product."*

There are clearly circumstances in which special at-risk populations must be evaluated for appropriate self-selection behaviors, particularly when the risk is substantial. However, there are important practical considerations, especially in cases where the prevalence of the contraindication is low and special methods must be employed to identify and recruit these people. Because there are both methodological and analytic pitfalls in enrichment, we recommend that additional guidance be provided on this point:

- As a general principle, self-selection studies should be all-comers (recruit a naturalistic sample of potential OTC users of the product), so that findings may be generalized to the population that will eventually select and use the drug.
- Where possible, special contraindicated populations should be studied in smaller, targeted trials, rather than the main self-selection study. If that is not feasible, and enrichment of the main study is necessary, the following issues should be considered:

    1. Recruiting at-risk populations is problematic because any advertising specific enough to target the correct group will almost inevitably sensitize prospective subjects to the very condition of interest, thereby influencing results.

    2. By definition, members of contraindicated populations cannot be correct selectors. Therefore, enriching a study with consumers who cannot appropriately select the drug may yield erroneous or misleading results, unless responses from those recruited via special population advertising can be identified and analyzed separately.

    3. Both the population prevalence of the condition and the clinical consequences of selection errors must be considered when weighing the outcomes in these at-risk groups. *A priori* performance standards should be selected accordingly.

89-90 *"…subjects who have relative or absolute contraindications…"*

The Draft Guidance does not currently draw a distinction between relative ('Ask a doctor before use') and absolute ('Do not use') contraindications, nor does it specify

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89-90 (cont.) which may appropriately be evaluated in self-selection testing. Absolute contraindications are clear candidates for evaluation in studies of this kind because their presence definitively renders consumers unsuitable for use. Relative contraindications, by contrast, are generally not amenable to testing in a self-selection study because appropriate selection depends on a *future behavior* (asking a doctor or pharmacist before taking the product), which cannot be adequately evaluated except in an actual use study.

122-124 *"Because… no drug product is administered in the study, exclusion criteria should be minimal…"*

It is important to acknowledge that sponsors have a broad set of tools, rather than just one basic design, to evaluate appropriate selection. For example, there may be circumstances in which providing a drug product in a self-selection study is the best way to evaluate selection behaviors (i.e. in cases where appropriateness depends on the nature of symptoms at the *time of use* rather than expectation of future symptoms at the time of purchase). A study design that evaluates consumers' ability to select or discriminate between products at the time of use is an important variation to consider for specific kinds of products.

Alternatively, selection may be best evaluated within the context of a larger actual use study, or in a separate, specialized validation study. The Guidance should clarify these points and leave open the possibility of selecting a combination of methods from a range of appropriate designs.

127-130 *"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."*

We clearly agree that consumers who read at a lower level are important to include in all studies for non-prescription products, and that careful consideration should be given regarding how best to ensure appropriate representation for this vulnerable sub-group. However, the following points should be considered:

1. The goal should be to collect low-literacy subjects in their true, naturally-occurring rate or proportion in the population (please note that studies we conduct without enrichment consistently capture 15-20% as defined by REALM). However, there are currently no national data for literacy as assessed using REALM or TOFHLA. Attempting to extrapolate low-literacy results from other national surveys (such as the National Assessment of Adult Literacy, or NAAL[1]) is inappropriate because the assessments represent fundamentally different constructs that measure different types of ability. Until reliable national data can be collected using REALM or TOFHLA, no meaningful estimate of the true low-literacy rate for these tools will be available to serve as a basis for evaluating correct representation.

2. There is no evidence to support the idea that lower-level readers are under-represented or excluded in a systematic way from national OTC studies. In fact, the opposite may be true; depending on the research setting and compensation, consumers of lower reading level may have equal or greater incentive to

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127-130 (cont.) participate than their normal-literacy counterparts (who often have higher education and income levels).

3. Compared to REALM, TOFHLA may be impractical as a tool for evaluating literacy in typical OTC studies. Average administration time for TOFHLA can be up to 22 minutes,[2] compared with 1-2 minutes using REALM.

4. There has never been information to suggest that key regulatory decisions depend on the performance of this particular group (poor readers) for whom the label was not designed (OTC Drug Facts labels have previously been acknowledged as written to an 8th grade reading level[3]). Therefore, enrichment or overrepresentation of this group in the sample likely does not contribute meaningfully to the overall approval decision.

141-142, 148-150 *"The primary endpoint for a self-selection study should be the proportion of the study subjects who make a correct self-selection decision" "In this case, a correct self-selection decision for a diabetic… would be that the drug product is not appropriate for his or her use."*

This current language implies two different kinds of denominators for calculating correction selection: 1) all subjects, and 2) subjects with specific contraindicated conditions. We agree that both may be useful ways to evaluate selection outcomes. However, focusing specifically on those who would be at risk from incorrect selection (subjects with contraindicated conditions on the label), may be the most helpful and relevant analysis of correct selection. In cases where the denominator is all subjects, it may be appropriate to exclude those who are suitable for use (do not have contraindicated conditions on the label) but who did not select the product (so-called "missed opportunity" subjects) from the calculation of correct selection, since this represents an "error" without risk.

160-163 *"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 understand and appreciate the rationale for this approach. However, it is important to acknowledge explicitly what this means and to encourage sponsors to select a pre-defined target or standard accordingly. Requiring that the lower limit of the confidence interval for the obtained value should exceed the target implies statistical *superiority*, rather than simply "meeting" the standard by demonstrating equivalence. This method creates an effective standard that (depending on sample size) is several percentage points higher than the stated target. This is fine, so long as expectations regarding the numeric standard are appropriately tempered.

Further, the pre-defined standard must be set at a level that will account or allow for sources of variation that are unavoidable in behavioral science studies of this kind. These sources of variation may include subjects' misunderstanding of the interview question asked, difficulty correctly articulating their responses, and interpretation and recording errors on the part of the interviewer, etc. These factors all combine to reduce or limit the maximum achievable success rate in any consumer study. Thus, it is important to recognize that correct selection findings will fall below 100% (and in some cases, well below) for reasons unrelated to understanding and

Line #(s):	Guidance Document Text / Comments:
160-163 (cont.)	heeding of label warnings. Finally, we believe that performance standards or targets should apply specifically to subjects of normal reading ability, or that separate, more realistic standards should be defined for low-literacy subjects. Results from the literacy groups should not be pooled for purposes of comparing to pre-defined targets.
169	*"Reasonable predefined mitigating factors may be acceptable in certain circumstances."* Allowing the opportunity to recast or re-categorize subjects' responses based on the full range of information they provide is an important element in correctly evaluating selection decisions. However, the term '*mitigation'* as used here implies only a one-directional change – from incorrect to correct, whereas a more scientifically-sound method is to evaluate all responses, both those initially considered correct and those initially considered incorrect, to determine if re-categorization is appropriate. Consequently, we recommend that a more neutral and less-biased term such as '*reclassification'* should be used to characterize the appropriate bi-directional nature of this analytic activity.
202-203	*"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…"* Selection endpoints should clearly be calculated for important subgroups of interest. However, as noted previously, we believe that different performance standards or targets should be defined for normal- and low-literacy subjects, and that these groups should not be pooled for purposes of evaluating selection decision endpoints. By definition, low-literacy subjects read at a level lower than the grade level at which the label is written, and thus by nature are expected to perform at a lower level than those who read well. Consequently, it makes little sense to hold both groups to a single standard.
269-270, 274-276	*"We do not consider purchase decision data to have any bearing on the interpretation of self-selection data or study outcomes… Because a purchase decision is generally influenced by cost, we consider it to be an unreliable surrogate for a self-selection decision."* One of the greatest challenges in any self-selection study is creating an environment that is sufficiently realistic to elicit meaningful responses from subjects. Because a consumer study without any actual medication is necessarily artificial, subjects often struggle to understand that they are expected to act exactly as they would if they were deciding right now whether to take a medication home from the store and use it for themselves. Hence, when asked a simple selection question ("Is it ok for you to use?") they reply yes, but when asked a follow-up question about whether they would purchase it, they reply, "no, of course not, because I have a condition listed under 'Do not use' on the label," or "no, because I don't have that symptom or condition right now, but if I did it would be ok to buy." The purpose of a purchase question and other similar elements is not to act as a surrogate for selection, but rather to improve the realism of the test and help participants

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269-270, 274-276 (cont.)	understand the true intent of the questions. Asking about selection in more than one way helps subjects move from purely hypothetical reasoning to more meaningful, concrete responses based on their own personal health situations. The language in the Guidance should be clear in addressing this need, and in specifying that purchase and other questions should not replace the primary selection question, but instead supplement and expand upon it. The quality of data collected in a selection study hinges on the believability and naturalism of the test. Clearly, the sequence of questions used to evaluate the selection decision and subjects' underlying reasoning must be carefully tailored to the label and unique objectives of the study. A single standardized approach will not suffice.
291-292	*"Response choices in multiple-choice questions should be independent and contain only one correct answer."* As a general principle, we believe multiple-choice questions are of limited value in consumer non-prescription research. Questions that require participants to generate meaning or content on their own (rather than simply selecting an existing answer option) provide a better opportunity to evaluate the reasoning that underlies product selection decisions.
312-313	*"The study site can be in a mall, or in other places frequented by consumers."* While a mall may be suitable for earlier stages of research involving a general (non-sufferer) consumer population, self-selection studies necessarily require actual sufferers and thus should be conducted in more realistic settings where consumers actually select OTC products. Rather than specifically identifying "a mall" in the Guidance (which may imply preference), we recommend more general language to encompass the range of suitable locations such as, "in an appropriate retail setting frequented by OTC consumers."
315-316	*"Also, a clinical setting may be appropriate in situations where lab tests are needed to verify [a] correct self-selection decision."* In some cases, subjects' self-reported medical history will be inadequate to reliably establish the presence or absence of a specific target condition. This is particularly true with non-symptomatic conditions (some of which have been considered for OTC switch), or conditions whose symptoms may be confused with more serious conditions. In these situations, a validation component, such as a laboratory test or diagnosis by a healthcare provider, may be required to evaluate proper consumer selection. Because this represents an important variation from the traditional self-selection design, it may warrant a separate heading and section in the Guidance Document (titled "Validation Studies"). This new section could include: • Examples of situations where validation may be needed. • A caveat that self-selection research requiring external validation should <u>not</u> be conducted solely in a clinical setting because of the potential to influence selection behavior (subjects in these settings often note they thought the product must be ok for them to use because the study was conducted in their doctor's office). • Instead, self-selection studies with a validation component should generally

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315-316 (cont.)	involve a selection decision in a realistic OTC-like setting, followed, where applicable, by a separate validation assessment (like physician exam or laboratory test) in a clinical setting.
322-324	*"Two general approaches to administering the questionnaire that can be considered include self-administration or asking the questions using a trained interviewer."* We believe self-administration is appropriate only in situations where the sensitivity of the topic or the presence of an interviewer will inhibit honest responses or otherwise prevent collection of good data. Unless this is the case, using a well-trained interviewer will yield both more and better-quality data in consumer studies, particularly in situations where careful, non-leading probing is needed to understand the reasons why subjects select or do not select the medication. In addition, problems with self-administration are intensified for subjects who read below normal level. In these cases, verbal administration by an interviewer may be indispensable.

CONCLUSION

We applaud the Agency's efforts to crystallize its views regarding self-selection study design and expound fundamental research principles that apply. The resulting dialogue with industry and release of the final guidance document will clearly advance the state-of-the-art in this critical area of non-prescription consumer research.

REFERENCES

1. The Health Literacy of America's Adults: Results from the 2003 National Assessment of Adult Literacy. Available from: URL: http://nces.ed.gov/pubsearch/pubsinfo.asp?pubid=2006483.

2. 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.

3. Label Comprehension, Self-Selection & Actual Use Studies: Issues & Challenges, Nonprescription Drugs Advisory Committee September 25, 2006, Andrea Leonard-Segal, MD, Director Division of Nonprescription Clinical Evaluation. Available from: URL: http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4230s1_01_01_%20Leonard-Segal.pdf.