Ref: Docket No. FDA-2011-D-0620 - Draft Guidance for Industry on Self-Selection Studies for Nonprescription Drug Products

To Whom it May Concern:

Thank you for the opportunity to comment on the Draft Guidance "Self-selection studies for nonprescription drug products". I believe that this Guidance will provide valuable assistance to the industry, and thus facilitate regulatory decision making by improving the quality of data submitted. I would like to highlight a few areas where I think additional clarification might be helpful.

The Draft Guidance does a very good job of emphasizing the potential importance of special populations in self-selection studies. While any inappropriate selection is undesirable, the most significant clinical consequences may result if a subject for whom the product is inappropriate due to a clinically relevant contraindication (absolute or relative) elects to use the product. As the Draft Guidance notes, an assessment of the label's effectiveness in discouraging such self-selection can only be assessed if consumers with the contraindication (relative or absolute) are studied. However, the Draft Guidance may be more effective if these concepts are included explicitly in aspects of the suggested Study Design. Specifically:

1. The suggested statement of the Primary Objective is too broad. It is my experience that this broad wording inhibits sponsors from focusing on the product-specific self-selection questions for which data are required to evaluate potential safety concerns and thus inform regulatory decision making. The Primary Objective should focus on those populations or decisions of most relevance. This has direct impact on trial design (for example ensuring adequate representation of the population of interest) and analysis (see below). It is the Primary Objective of any study that guides the design, not the reverse. It is the starting point. By helping sponsors to focus it is my opinion that study relevance and quality will be enhanced and innovation encouraged. I also realize that the reviewers will be broadly interested in self-selection behaviors, but these can be secondary objectives and should not dilute the design elements to address the most clinically relevant issues. I further realize that each point made above is made directly or indirectly in other sections of the Draft Guidance (for example lines 120-122), but I believe the emphasis and prioritization is critical to optimizing the data collection process and bringing FDA and sponsors perspectives into alignment. Of course, if there are no populations of special concern the broader language may be appropriate, but the rationale for the self-selection study under these circumstances would still merit explicit statement as part of the primary objective.
2. The data analysis should also reflect the logic of focusing on the specific questions of interest. Thus, the use of the total population as the denominator for the primary analysis has the potential to mask incorrect self-selection of high importance. The analysis plan should reflect the pre-specified clinically important questions and the Primary Objective(s) as discussed above. Thus, if it is important that consumers with condition X not self-select, the calculation should be the number of subjects with condition X who self-selected divided by the total number of subjects with condition X. Further, a pre-specified threshold for the acceptable rate of inappropriate self-selection should be established based on the clinical consequences of use of the drug by consumers with condition X. Use of the larger denominator (total subjects) dilutes the ability to address the issues most important for consumer safety. Further, in my experience sponsors often mislead themselves, and try to mislead others, by appearing to have a very high success rate during self-selection by recruiting a cohort for whom the drug is either appropriate

or for whom use of the drug poses little clinical risk. It may be argued that this means there would be little risk in the general consumer population, but that logic is faulty due to the small sample sizes used and the recruitment biases. If safety in the general population is dependent on decisions made by subsets of the population, the self-selection study must be focused on these cohorts. Ambiguity on this point in the Guidance will only lead to lack of clarity in trial designs. The analysis (and objective) proposed in the Draft should only be the default if no more focused questions are relevant.

A second area of concern is the formatting of the study's pivotal question to consumers. In lines 45-47 the Draft Guidance states: "…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…" I believe that this overstates the case. To my knowledge there are no data that establish that a self-selection "right for me" decision is predictive of use by the consumer. Rather, in my view, data from actual use trials that included a self-selection component suggest that there is a hierarchy of consumer decisions: the broad "right for me", then purchase, and then use. Each of these three decision points involves increasing "stakes" for the consumer, moving from a theoretical decision, to a decision requiring financial expenditure, to actual exposure to the drug. The stakes are likely to increase the rigor of analysis by the consumer. This is supported by studies showing that some consumers who think the product is right for them sometimes will not purchase, and some who purchase will not use. The responses of these subjects to open ended question suggest an increasing focus on the label information as the stakes increase. This differential level of decision making is further confounded by potential confusion around the pivotal question. On line 236 the Draft Guidance suggests as the pivotal question: "Is it okay for you to use this medication?" However, it is easy to imagine a consumer being confused by this. Does the question apply based on their current condition or at some point in the future? Does it mean simply do they have the label indication or does it mean they meet ALL label requirements? When asked without cuing (as would be appropriate) consumers may not take the question as seriously or as comprehensively as intended. Again, data from open-ended responses in previous studies supports this conjecture. Thus, to state on line 268 that the purchase decision has "no bearing" is an over simplification. In my opinion there should be flexibility based on the relevant clinical issues to use the endpoint suggested in the Draft, or a purchase decision or a use decision (or more proximal surrogate). Whatever is chosen needs to be justified and discussion of the rationale with the Agency would be appropriate before finalizing the trial design.

Finally, I would like to comment on the issue of mitigation, particularly as related to the pivotal question. I have observed different "expectations" amongst sponsors as to the threshold for mitigation. I would suggest that the Guidance offer four standards for mitigation: 1) the mitigation should be clinically reasonable, 2) that the rules for mitigation be prospectively defined, 3) that the algorithm for mitigation be as objective as possible, and 4) that mitigation decisions be auditable. This last criterion means that a third party could review the protocol, the collected data (including the open-ended responses) and reach the same conclusion as sponsor. I believe that this would ensure agreement before the trial as to what is clinically relevant mitigation and ensure a more objective regulatory review. In this context I would also suggest that two types of open-ended questions be permitted: The first would be highly structured and could be used for mitigation and data-analysis purposes. The second would be explicitly probing, particularly for consumers who inappropriately self-selected. This second type of question would not be used for meeting primary study objectives, but rather would be an effort to get at root-causes of inappropriate self-selection. This information might be extremely valuable for sponsors and the FDA both for the specific-product review but also in developing generalizable expertise and experience.

Thank you for the opportunity to comment on the Draft Guidance and I would be happy to amplify or clarify any of the above points.

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