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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm.1061
Rockville, MD 20853

Re: Docket No. FDA -2011-D-0620 -Draft Guidance for Industry: Self-Selection Studies for Nonprescription Drug Products

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., is a leading worldwide human health products company. Through a combination of the best science and state-of-the-art medicines, Merck's Research and Development (R&D) pipeline has produced many important pharmaceutical products in both the prescription and nonprescription products available today. Our consumer health division, Merck Consumer Care (MCC), has decades of experience in providing over-the-counter (OTC) healthcare products to U.S. consumers, including conducting Rx-to-OTC switch programs.

General Comments

We commend the Food and Drug Administration (hereafter referred to as the FDA or the Agency) for its efforts in developing a comprehensive approach to the design and evaluation of self-selection studies for OTC products and for products being studied for a switch from Rx to OTC status. The topic of self-selection studies and of consumer behavior studies in general, is of critical importance to the Agency, the consumer health products industry, and the contract research companies that often conduct such studies. The science behind consumer behavior studies, including self-selection studies, has evolved considerably over the past decade, both through the efforts of companies to design studies that better answer the relevant questions and through collaboration between FDA and industry to better define what is required from these studies. We appreciate the Agency's efforts to guide industry in designing and conducting scientifically rigorous studies that will best examine the ability of consumers to use these products safely in an OTC environment. We also encourage the continued collaboration between FDA and industry to further elucidate the best ways to conduct this research, including a continuation of the types of meetings, seminars, and workshops that have been so successful thus far.

We understand that the Consumer Healthcare Products Association (CHPA) will be providing an overall industry response to the draft guidance. We endorse and support the CHPA on this issue. We also believe that our own comments will contribute additional value to the Agency's understanding of the industry's perspectives. We are pleased to have this opportunity to add our insights to the guidance based on our extensive experience in designing and conducting studies of this type.

Specific Comments

We agree with many of the Agency's positions as stated in the draft guidance, and find that they reflect the way we currently conduct these studies. We do, however, find a few areas that we feel could be clarified or modified, as addressed in detail below.

Again, we appreciate the opportunity to comment on the Agency's Draft Guidance for Industry: Self-Selection Studies for Nonprescription Drug Products. For further information or questions, please contact me by phone at 908-423-7768, or email janet_vessotskie@merck.com.

Sincerely,

Janet Vessotskie PhD, MPH
Director, U.S. Regulatory Policy
Global Regulatory, Strategy, Policy and Safety

Page and Line No.	Comments and Recommendation
A. Purchase Decision **Page 7, lines 269-276:** 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.	We believe that purchase decision is a useful adjunct that allows a fuller understanding of the self-selection decision made by some subjects. In our experience, the self-selection question ("Is this product appropriate for you to use or not?") is viewed by some subjects as abstract and not relevant to their real-world situation. However, the purchase decision question ("Would you like to purchase this product right now for your own use or not?") is better understood by some subjects as applying to them in a very real fashion. It is more akin to the question they ask themselves when selecting a product in a pharmacy. The reasons given by the subject for their answers to both questions can serve to clarify the thought process they used in assessing the product. **Recommendation**: Modify the above paragraph to allow purchase decision data to be used as supportive information. **Justification:** In many cases, a subject's self-selection and purchase decisions are the same. They feel the product is appropriate for them to use, and they wish to purchase it, or they feel it is not appropriate for them to use, and they decide not to purchase it. In some cases, however, a subject may say the product is appropriate for them to use, but decide not to purchase it. This can be termed "withdrawal," in the sense that the subject is withdrawing from the initial self-selection decision. In other cases, a subject may say the product is not appropriate for them to use, but decide they will override this decision and purchase it anyway. Both withdrawal and override decisions can give us insight into how the subject is thinking and how they might act in a real-world pharmacy setting.

	We agree that a purchase decision alone should not be allowed to mitigate an incorrect self-selection decision, although other data, such as responses to open-ended questions, are often available to augment what we know from the self-selection and purchase decisions. We also agree that an important component of consumer behavior studies, including self-selection studies, is the open-ended questions that ask the subjects the reasons for their decisions ("Why did you say that?"). These responses give valuable insight not only into how a subject is making decisions, but also into how well they understand what is being asked of them. In our most recent application to switch MEVACOR™ (lovastatin) from Rx to OTC status (2007), we presented the results of a self-selection study that was modeled as an actual use study entitled Self Evaluation of Lovastatin to Enhance Cholesterol Treatment (SELECT) in order to obtain both self-selection and purchase decision data from subjects [1]. The subjects were not told until the end of the study, after all questions had been answered, that the product was not actually available for purchase. This study presents a large data set, with approximately 1499 subjects, of whom 1324 completed the study according to the protocol. We have conducted a *post hoc* analysis (not included in the application and not published) of the self-selection and purchase decisions made in the study. We present here a few relevant insights from that analysis that we feel support the position that purchase decision can be useful in determining the motivations and intentions of consumers. The draft guidance states that "a purchase decision is generally influenced by cost." In the SELECT study, we found that approximately 20-25% of subjects with a withdrawal decision mentioned cost as a factor in that decision. Note that because the response was open-ended, the subjects were able to list multiple reasons for their decisions, and were not limited to choosing the most important reason. The majority of subjects did not mention cost as a factor in their decision at all.

	However, a substantial proportion (approximately 30%) stated that they did not wish to purchase because they did not meet the eligibility requirements, despite having stated that the product was right for them. This shows that these subjects did not understand the self-selection question, but did understand the label directions and intended to act correctly according to them. Most subjects who withdrew due to eligibility and who were actually ineligible to use the product were ineligible because of the label directions related to safe use of the product, rather than the criteria related to achieving the correct benefit. Approximately 25-30% of subjects indicated that they did not wish to purchase the product because they wanted to consult with a physician or other healthcare provider first. They had stated that the product was right for them, but their purchase decision indicated they were uncertain and wanted to make sure they were deciding correctly whether to use the medication. The type of understanding illustrated by these examples should be allowed to mitigate a self-selection decision that, on its face, was incorrect. On the other hand, subjects who choose to override an otherwise correct negative self-selection decision may be found to be incorrect. However, in assessing the risk-benefit equation for the product in question, it can be valuable to determine why the subjects made this override decision. In our study, the majority of subjects who made an override decision were ineligible for the product because they would not derive an appropriate benefit, but did meet all safety-related eligibility criteria. It is important to know that these subjects would not put themselves at undue risk from use of the product, even if they did not achieve optimal benefit. It is also valuable to know that the rate of override decisions was much lower than the rate of withdrawal decisions. These results show that for some subjects, the purchase question is more easily understood than the self-selection question, and they consider it more carefully

	because it relates more to their actual situation. Analysis of the subject's open-ended responses and of their actual eligibility, as determined by their self-reported medical history and conditions, allows us to more fully understand the context of these decisions and what they might mean in the real-world marketplace. When a subject's responses clearly indicate that they did not correctly understand the self-selection question, these responses and the purchase decision should mitigate an otherwise incorrect response, just as they may render an otherwise correct decision invalid. Data that can clearly help us better understand the way consumers would use a product in the marketplace should not be discounted based on the assumption that cost is usually a major factor in the subject's decision-making process.
B. Low-Literate Representation **Page 4, lines 128-134:** 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, REALM-Teen for testing adolescents or the Test of Functional Health Literacy in Adults (TOFHLA or S-TOFHLA).	We agree that education level is not a valid surrogate for literacy level, because scores achieved by study subjects on the validated screening instruments mentioned in the text above do not always correlate closely with the education level reported by those subjects. We also agree that the screening instruments mentioned are the best tools currently available for determining study subjects' health literacy levels within the context of a self-selection study or other consumer behavior study (such as label comprehension or actual use studies). **Recommendation:** The first sentence quoted above is vague, in that it does not provide guidance about the type of "national data" to be used or about the definition of "basic literacy skills." The draft guidance should be clarified. In addition, we encourage the FDA to discuss these issues at public workshops with industry and other stakeholders to reach a resolution. **Justification:** We are concerned that this ambiguity could be interpreted to refer to the health literacy data from the National Assessment of Adult Literacy (NAAL), conducted periodically by the National Center for Education Statistics (NCES), an agency of the

	U.S. Department of Education. The NAAL results published in 2006 [2] have been cited in the past by FDA in requesting a certain proportion of study subjects that should be low literate, and the report does use the term "basic" as one of the literacy levels defined in the results. The REALM and TOFHLA instruments are commonly used to screen for low-literate participants in consumer behavior studies. The NAAL is a very different instrument than the REALM or TOFHLA. It asks different types of questions, it measures different aspects of literacy and health literacy, and it uses different groups and cutoffs to define the different levels of literacy. Therefore, it is not valid to use the NAAL data to determine the proportion of low-literate subjects in a study, but use the REALM or TOFHLA to screen for those subjects. However, the NAAL instrument cannot be made available for use in consumer behavior studies in order to maintain its validity in future NCES surveys, and would not be practical for this use due to its length. There have been no studies to date that correlate the literacy levels measured by the NAAL with scores on the REALM and TOFHLA, and lack of access to the NAAL instrument prevents academic or industry researchers from conducting such studies. Another issue with using the NAAL data to determine low-literate representation is that the NAAL data report does not use the term "low literate." There is no consensus as to whether the Basic or Below Basic level correlates with the term "low literate," nor with which of these levels correlates with the literacy level required to read and understand an OTC Drug Facts label. There are no national data regarding the proportion of the U.S. population with low health literacy skills as determined by REALM or TOFHLA. The accepted REALM score that indicates low literacy is 60 or less (i.e., more than six words pronounced incorrectly). Anecdotal evidence from several companies that produce consumer healthcare products and contract-research companies that conduct consumer behavior studies indicate that approximately 15% of participants in most such studies are found

	to be low literate using the REALM tool. It is uncertain how closely this figure correlates with what would be found in a representative sample of the entire U.S. population. Given the uncertainties with how to apply the NAAL data to consumer behavior research and the lack of correlation with the screening tools used in such research, it is not valid to use the NAAL data to determine the proportion of study subjects that should be low literate. There are no national data regarding the proportion of low literacy abilities in the U.S. that can be correlated with the literacy screening tools used in consumer behavior research. However, the draft guidance does not mention the disparity between the NAAL data and the application of those data when using the other screening tools currently in use. As such, we suggest that this section of the draft guidance be modified to address these concerns.
C. Definition of Mitigating Factors **Page 5, lines 180-182:** 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. AND **Page 7, lines 264-266:** 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.	We agree that, to the extent possible, factors that would mitigate an otherwise incorrect self-selection decision should be specified prior to the start of the study. However, given the variability of responses to open-ended questions, it is not possible to anticipate every possible response that study participants may give. Therefore, we feel it is important to maintain the flexibility to determine that an unanticipated response given during the study may be used to mitigate an otherwise incorrect self-selection decision. **Recommendation:** We suggest that the above statements be modified to indicate that mitigating factors should be pre-specified as much as possible, but that other factors may be found to be mitigating *post hoc*.

D. Self-Selection as Part of an Actual Use Study **Page 2, lines 70-71:** *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.*	We agree that actual use studies are outside the scope of this guidance. However, we recognize that in some instances, it may be appropriate and desirable to include self-selection as a component of an actual use study. **Recommendation:** We encourage FDA to address this issue in the guidance document for actual use studies that is expected in the future.

References

1. Brass EP, Vassil T, Replogle A, Hwang P, Rusche S, Shiffman S, Levine JG. Can consumers self-select for appropriate use of an over-the-counter statin? The Self Evaluation of Lovastatin to Enhance Cholesterol Treatment Study. Am J Cardiol 2008; 101:1448-1455.

2. Kutner M, Greenberg M Ying J, Paulsen C, White S. The Health Literacy of America's Adults: Results from the National Assessment of Adult Literacy (NCES 2006-483). 2006. U.S. Department of Education, National Center for Educational Statistics. Washington, DC: U.S. Government Printing Office.