Supporting Statement for

Experimental Study: Toll-Free Number for Consumer Reporting of Drug Product Side Effects in Direct-to-Consumer Television Advertisements for Prescription Drugs

Submitted by

Center for Drug Evaluation and Research
Office of the Commissioner

Food and Drug Administration

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A. JUSTIFICATION

1. Circumstances Making the Collection of Information Necessary

Section 1701(a)(4) of the Public Health Service Act (42 U.S.C. 300u(a)(4)) authorizes the Food and Drug Administration (FDA) to conduct research relating to health information. Section 903(b)(2)(c) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 393(b)(2)(c)) authorizes FDA to conduct research relating to drugs and other FDA regulated products in carrying out the provisions of the FD&C Act.

On September 27, 2007, the President signed into law the Food and Drug Administration Amendments Act (FDAAA, Public Law 110-85). Title IX of FDAAA amends section 502(n) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 352) by requiring printed direct-to-consumer (DTC) advertisements for prescription drug products to include the following statement printed in conspicuous text: "You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088." Title IX of FDAAA also requires the Secretary of Health and Human Services (Secretary), in consultation with the Advisory Committee on Risk Communication, to conduct a study not later than six months after the date of enactment of FDAAA to determine if this statement is appropriate for inclusion in DTC television advertisements for prescription drug products. As part of this study, the Secretary shall consider whether the information in the statement described above would detract from the presentation of risk information in a DTC television advertisement. If the Secretary determines that the inclusion of such a statement would be appropriate for television advertisements, FDAAA mandates the issuance of regulations implementing this requirement, and for the regulations to reflect a reasonable length of time for displaying the

statement in television advertisements. Finally, FDAAA requires the Secretary to report the study's findings and any subsequent plans to issue regulations to Congress.

In accordance with the requirements of FDAAA, FDA convened a meeting of the Risk Communication Advisory Committee on May 15-16, 2008. A draft design for studying this issue was proposed at that time and discussed by the Advisory Committee. Based on comments received at that meeting, changes were made to the proposed study design. The transcripts and materials from that meeting can be found online at http://www.fda.gov/ohrms/dockets/ac/oc08.html#RCAC.

Relevant Prior History and Research

Section 17 of the Best Pharmaceuticals for Children Act (the BPCA) (Public Law 107-109, January 4, 2002) required FDA to issue a final rule mandating the addition of a statement to the labeling of each drug product for which an application is approved under section 505 of the Act. Under the BPCA, the statements must include: (1) a toll-free number maintained by FDA for the purpose of receiving reports of adverse events regarding drugs; and (2) a statement that the number is to be used only for reporting purposes, and it should not be used to seek or obtain medical advice (the side effects statement).

On April 22, 2004, FDA published a proposed rule with a proposed side effects statement for certain prescription drug product labeling and a proposed side effects statement for certain over-the-counter drug product labeling (69 FR 21778). In the proposed rule, FDA solicited comments on a proposed statement that FDA believed comported with the above mandate in the BPCA. The Agency received 12 comments suggesting changes to the specific wording proposed. The agency also received several comments suggesting that FDA engage in research to study the wording of the proposed side effects statement with consumers. Among the reasons

cited for testing the statement were: (1) to determine the best and most precise wording for the statement; (2) to evaluate consumer comprehension of the proposed statement; and (3) to address concerns that consumers who read the statement will mistakenly call FDA in search of medical advice rather than seeking appropriate medical treatment. In addition, during the clearance process for the proposed rule, both the Office of Information and Regulatory Affairs of the Office of Management and Budget (OMB) and the Office of the Assistant Secretary for Planning and Evaluation (ASPE) of the Department of Health and Human Services suggested that FDA conduct focus groups or other consumer studies to inform the wording of the side effects statement.

During the spring of 2006, to assist in developing this study, FDA conducted two focus groups to gauge consumer understanding and preferences for a number of proposed side effects statements and to narrow the number of statements to be tested in subsequent experimental research. In addition to the information collected on which versions of the statements participants preferred, discussions showed that people varied in their understanding of when to call FDA or their practitioners and that some people would not call FDA even if they experienced a serious side effect. Several people in the focus groups suggested the addition of a website to report adverse side effects.

Based on the findings from the focus groups, nine statements were selected for quantitative testing. A labeling comprehension experiment was conducted with 1,674 men and women ranging in age from 21 to 95 with varying levels of education (OMB Control No. 0910-0497). The results from that quantitative test found that only one of the versions tested was rated as significantly less clear than the others, which were all rated as generally clear and understandable. The results also showed that participants reported they would not call FDA

seeking medical advice. Further, among those participants who said they would call the FDA, the majority indicated they would call their doctor for medical advice, rather than FDA, regardless of the severity of the side effect. Finally, participants indicated they could distinguish between serious and non-serious side effects, reporting that they would seek emergency medical care in the case of serious side effects. The report of the study is available in the docket for the final rule, Docket No. FDA-2003-N-0313. The final rule, *Toll-Free Number for Reporting Adverse Events on Labeling for Human Drug Products* (73 FR 209, October 28, 2008), is available online at http://frwebgate6.access.gpo.gov/cgi-bin/PDFgate.cgi?WAISdocID=378215277140+0+2+0&WAISaction=retrieve.

2. Purpose and Use of the Information Collection

The purpose of this study is to address the requirements of Congress as written in Title IX of FDAAA. Instead of automatically requiring the statement in television ads, Congress specified that research shall be conducted to address the issue of whether the inclusion of the toll-free statement will detract consumers from the risk information in the ads. This study, along with other considerations of public health issues and an analysis of MedWatch considerations, will determine whether the toll-free statement will be required. Specifically, if the research shows that the toll-free statement does not detract from the understanding of risk information at all, its inclusion in television ads is likely to be mandated. If, on the other hand, some detraction is demonstrated, then public health concerns and MedWatch considerations will play a larger role in determining whether the benefits of the inclusion of the statement outweigh the detraction from the risk information.

3. Use of Improved Information Technology and Burden Reduction

Automated information technology will be used in the collection of information for this study. The contracted research firm will collect data through Internet administration. The participant will self-administer the Internet survey via a computer, which will record responses and provide appropriate probes when needed. In addition to its use in data collection, automated technology will be used in data reduction and analysis. Burden will be reduced by recording data on a one-time basis for each respondent, and by keeping surveys to less than 20 minutes.

4. <u>Efforts to Identify Duplication and Use of Similar Information</u>

Although some previous studies have investigated various aspects of print DTC ads,[1] little published research has been conducted on television DTC ads. Published research has typically used content analysis and not rigorous experimental investigation.[2] Such research does not permit extrapolation to understanding consumers' perceptions or intended behavior.

As described in Section A1 (*Circumstances Making the Collection of Information Necessary*, p. 5) FDA completed a study examining the wording of a toll-free statement to be placed on prescription and non-prescription drug labels.[3] Aside from this usability study, which applied to printed material and not broadcast media, FDA is not aware of previous research on the role of a side effect-related statement in DTC ads.

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[1]See, for example:
Holmes, E.R. & Desselle, S.P. (2004). Evaluating the balance of persuasive and informative content within product-specific print direct-to-consumer ads. *Drug Information Journal, 38*, 83-98.
Munce, S.E., Robertson, E.K., Sansom, S.N., & Stewart, D.E. (2004). Who is portrayed in psychotropic drug advertisements? *The Journal of Nervous and Mental Disease, 192*, 284-288.

[2]See, for example:
Kaphingst, K.A., DeJong, W., Rudd, R.E., & Daltroy, L. (2004). A content analysis of direct-to-consumer television prescription drug advertisements. *Journal of Health Communications, 9*, 515-528.
Kaphingst, K.A., Rudd, R.E., DeJong, W., & Daltroy, L. (2005). Comprehension of the information in direct-to-consumer television prescription drug advertisements among adults with limited literacy skills. *Journal of Health Communications, 7*, 609-619.
Sumpradit, N., Ascione, F.J., & Bagozzi, R.P. (2004). A cross-media content analysis of motivational themes in direct-to-consumer prescription drug advertising. *Clinical Therapeutics, 26*, 135-154.

[3] The report of the study is available in the docket for the final rule, Docket No. FDA-2003-N-0313. The final rule, *Toll-Free Number for Reporting Adverse Events on Labeling for Human Drug Products* (73 FR 209, October 28, 2008), is available online at http://frwebgate6.access.gpo.gov/cgi-bin/PDFgate.cgi?WAISdocID=378215277140+0+2+0&WAISaction=retrieve.

5. **Impact on Small Businesses or Other Small Entities**

No small businesses would be involved in this data collection.

6. **Consequences of Collecting the Information Less Frequently**

The proposed data collection is one-time only. There are no plans for successive data collections.

7. **Special Circumstances Relating to the Guidelines of 5 CFR 1320.5**

This collection of information fully complies with 5 CFR 1320.5. There are no special circumstances.

8. **Comments in Response to the Federal Register Notice and Efforts to Consult Outside the Agency**

The 60-day public comment notice was published in the Federal Register on November 26, 2008, Volume 73, Number 229 (Docket No FDA-2008-N-0595). A copy of the 60-day Federal Register notice is included as Attachment 1.

FDA received six comments in response to our initial federal register notice, published on November 26, 2008. One of these comments, from an anonymous citizen, did not require specific responses, as it was outside the scope of the project (e.g., FDA approves too many drugs; harmful drugs are "being foisted on the population"), although it could be viewed as a statement of support for conducting the research.

In the following section, we outline the issues raised in the comments and provide our responses.

Angela Stanton, Ph.D.

Dr. Stanton does not recommend the placement of the toll-free statement in television ads because she feels they are better placed within written materials that accompany prescription

drugs. She recommends that some system for enforcing the legitimacy of calls is necessary, otherwise callers with an "agenda" or "the uninformed" could "doom medicines for no reason."

We thank Dr. Stanton for her comments. They mostly apply, however, to MedWatch procedures that are outside the scope of the proposed research. This study is addressing the understanding of information in the ad. We have notified the appropriate parties in the Agency of her comments.

American Society of Health-System Pharmacists (ASHP)

ASHP supports DTC advertising that is educational and "delayed until postmarketing surveillance data are collected and assessed," and believes that DTC television ads *should* include a toll-free statement. Overall, they support the proposed research, but have the following specific suggestions.

ASHP disagrees that the statement is best placed after the risk information. They suggest that it be placed during the presentation of non-life-threatening or minor side-effects. We agree that placement during non-life-threatening or minor side effects may be the best placement for the toll-free statement. Realistically, however, in a television ad, that information is presented in a very short amount of time, sometimes only seconds (and this varies depending on drug product). We have designed our study to allow the data to show for us what the best placement of the statement will be.

ASHP is concerned that neither of the proposed toll-free statements addresses whether consumers can distinguish between serious and non-serious side effects. They suggest a simulation study to assess this issue. We refer this commenter to previous research conducted by FDA on this topic, described in Section A1 (*Circumstances Making the Collection of Information Necessary,* p. 5). This study found that participants were easily able to distinguish

between serious and non-serious side effects and that they reported an ability to take the right action with regard to each one.

The remaining three comments were more detailed and raised several distinct points. For these comments, we will list the concern and our response to it individually.

Pharmaceutical Research and Manufacturers of America (PhRMA)

• Transparency and Validity of Protocol: PhRMA suggests that we post the proposed questionnaire, the primary endpoint(s) of the study with action standards, and provide the mock advertisement to interested parties for use in their research.

Response: The proposed questionnaire has been and continues to be available upon request. We agree that threshold levels and primary endpoints were not well explained in the 60-day notice and have worked to correct that in the 30-day notice. Please note the addition of specific hypotheses and the analysis plan. At the conclusion of our data collection, we will make the advertisement available to those who request it.

• Transparency and Accuracy of Stimuli Ads: PhRMA expressed concern that adequate provision issues will not be considered or addressed and that multiple telephone numbers or websites may confuse consumers. They also suggest alternate wording for the toll-free statement: "For information about PRODUCT X or to report side effects, see our ad in _____ magazine." Finally, they encourage the inclusion of payment assistance information, as this is often currently included in television ads.

Response: We have designed the stimuli ad to closely approximate an actual DTC ad—including adequate provision measures and other supers. DDMAC reviewers have examined the script and storyboard to ensure that the ad meets regulatory requirements. The contractor producing the ad has extensive experience with this type of production

and provided additional quality control measures. In directing us to complete this research, Congress was likely concerned about the same issues expressed by this commenter: i.e., that the toll-free statement may be confusing. That is one of the main research questions we will address. In terms of wording, Congress directed us to test specific language. In addition to this language, we propose to test another version that was found most acceptable in previous usability research conducted by the Agency. Finally, because payment assistance information is relatively new, not universal, and not required by regulation, we have not included this statement in our stimuli ads.

FDA has contracted with a professional multimedia company to create ad stimuli. In addition, FDA has instituted a procedure of extensive pretesting of the ad stimuli to be used. Our extensive experience with current and past DTC ads, pretesting, and collaboration with the contractor should ensure realistic ads that will enable us to successfully investigate our experimental variables.

• PhRMA recommended studying: multiple medical conditions including symptomatic and asymptomatic ones; diseases that affect different age groups; sufferers and non-sufferers; and consumers with varying about of knowledge.

Response: We do not have the resources to create mock ads to test multiple medical conditions. We see no a priori reason that the principles we study in this medical condition (e.g., placement, duration, wording, prominence) would be different applied to an ad for another medical condition. We welcome other parties to extend the current research by applying it to other conditions. We will ask respondents about their knowledge of their medical condition and will conduct analyses to see if this variable plays a role in their responses.

We have decided, however, to recruit for the study two distinct populations: those who have been diagnosed with high blood pressure and a general population sample. This approach will allow us to determine whether diagnosed individuals and other people who may be exposed to such television advertising will differ in their responses to the ad.

• PhRMA is concerned that using the condition where the toll-free statement is present during the whole ad to control for novelty will increase rather than decrease the attention to the statement.

Response: We agree that the condition in which the toll-free statement appears during the entire ad may increase notice of it. We think there is also a good possibility that it might cause a wash-out effect, in such a way that the statement might be more prominent in other conditions. To control for novelty, participants will see an unrelated DTC ad with the toll-free statement presented the same way as the test ad before they see the test ad. This may control for novelty in the test ad and may attenuate the belief that our test product has some unique quality that causes it to need a special toll-free statement.

• PhRMA is concerned that this protocol will take much longer than 15 minutes.

Response: We are also concerned that this protocol will take longer than 15 minutes, so we have revised our burden estimation to reflect a 20 minute protocol. Also, we have budgeted for two pretests of 700 individuals each to make sure that all test parameters are met, including timing of experiment.

sanofi-aventis

• The placement variable should be removed from study because regardless of placement, the statement may interrupt the flow of the most important information.

Response: This is an empirical question.

• The duration variable should be removed from the study because regardless of duration, the statement may interrupt the flow of the most important information.

Response: This is an empirical question. We will not know the answer to either of these questions until we collect data.

• sanofi-aventis recommends removing the audio-only condition because this eliminates hearing-impaired population. They also recommend including visually and hearing impaired to more accurately represent the population.

Response: Even in our audio-only condition as originally proposed, the website and phone numbers were placed on screen. That said, current requirements for the most important risk information, i.e., the major statement, are that it be placed in the audio portion of the ad. Thus, this is a reasonable condition to test. Upon further discussion, however, we agree that we do not need two distinct extra-prominent conditions, and will test only one. We do not plan to actively exclude people with audio or visual impairments from the study but we do not have the resources to actively recruit them.

• High blood pressure may not be the most representative condition for a general sample of consumers over the age of 18. The tested sample population should be representative of actual sufferers of the condition being advertised.

Response: Merck also mentioned this concern and we agree that this is an important consideration. Upon further discussion, we have decided to recruit for the study two distinct populations: those who have been diagnosed with high blood pressure and a general population sample. This approach will allow us to determine whether diagnosed individuals and other people who may be exposed to such television advertising will differ in their responses to the ad.

• sanofi-aventis does not believe the 4th commercial for an unrelated medical condition contributes to the study and may confound results and so suggests removal.

Response: Respondents will see four ads—the 2nd ad will be an unrelated DTC ad and 4th ad will be the test ad. We propose to include the other DTC ad with the matching toll-free statement parameters so that consumers do not think that our test ad reflects a special product that needs a special warning. It also may attenuate the effect of novelty.

• Since the toll-free statement may artificially increase impact of risk information, FDA should test information gleaned from the presence of the toll-free statement in print ads first.

Response: FDA has not collected any information on the presence of the statement in print ads, although we agree this would be valuable information. Moreover, Congress has instructed us specifically to test the toll-free statement in television ads.

• Including the manufacturer's toll-free number instead of the FDA contact number may help to mitigate the possibility that the toll-free statement artificially increases the impact of risk information.

Response: Sponsors already include the manufacturer's telephone number in all ads as a way to fulfill one part of the adequate provision requirement. The current study does not examine the replacement of that number with the toll-free statement, but instead the statement's inclusion above and beyond current requirements.

• Agency's expectation of yielding a sample of 2,000 people from a total of 2,400 is unrealistic based on a typical response rate of 5%.

Response: We do not expect to yield a sample of 2,000 people from a total of 2,400. As shown in the burden chart in Section A12 (p. 18), we have revised our sample numbers.

• sanofi-aventis expressed concern about how well an internet study can simulate a television environment.

Response: We agree that simulating an everyday television-watching environment would increase the realism of the study. Realistically, however, participation in an experiment in any context is unlikely to perfectly do so. We do not believe that a mall-intercept administration would increase the realism of the study and a phone-based survey is not feasible, given the modality of the advertisement in question. Moreover, an internet study may be as close to the television-watching environment as any other method, since participants will be in their own homes and some participants already watch streaming video on their computers.

• Will there be thresholds to identify the outcome of success for each question? Will it be the best response or will there be a level of positive responses that meet pre-specified criteria the Agency will deem acceptable in decision making?

Response: As mentioned in Section A2 (*Purpose and Use of the Information Collection*), if the study demonstrates that the inclusion of the toll-free statement does not interfere with the processing of the risk information, then Congress is likely to mandate its inclusion. If the data demonstrate *some* detraction from risk information, then the decision becomes more complicated. Certainly the more the statement interfered with the risk information, the less likely it is that it would be mandated. A tradeoff analysis will have to be conducted and this study will be only one part of the determination. That is, the amount of detraction will have to be weighed against the benefit of including the statement and this benefit will be determined in part by public health concerns and analysis of MedWatch data.

• sanofi-aventis is concerned that participants will see the test ad three times and that this may cause problems.

Response: Participants will see the test ad only once after seeing three other filler ads, one of which will be an unrelated DTC ad.

Merck

• Current proposed study is comprehensive and appropriate to address the primary research questions under consideration.

Response: Thank you.

• The toll-free statement in the unrelated DTC ad should be presented in the same way as in the test ad.

Response: We had planned to do so.

• The current sampling strategy will likely not include enough people who have high blood pressure and the content of the ad will not be salient to people who do not consider themselves at risk for the condition. Merck recommends screening for people who have or are at risk for high blood pressure.

Response: See above, (page 12 of this document), under response to similar comment from sanofi-aventis.

• The questionnaire does not specifically address the risk of non-treatment of the disease-condition.

Response: FDA acknowledges that this study does not address this risk. Nevertheless, this is outside the scope of the current investigation.

• Merck recommends asking if respondents suffer from diabetes, high cholesterol, obesity, or the condition treated in the unrelated DTC ad.

Response: FDA had planned to ask about the state of respondent's health. In considering this comment, we have added some additional questions to the questionnaire. Please see the revised questionnaire for details.

• Specific comments about questionnaire items.

Response: Thank you for your attention to the questionnaire. We have rearranged the questionnaire so that what was question 7 is now asked before any substantive questions. We do feel, however, that the wording of this question should remain vague. One purpose of the study is to determine whether people can recall the toll-free statement amidst adequate provision items, other supers, and other information. Thus, we do not want to specifically probe them for the statement by cueing them to the toll-free statement. We have made small wording changes to the question as well as other changes to the questionnaire to more closely reflect our goals. Please see the revised questionnaire for details.

• It is unclear how FDA plans to analyze results from this research, particularly what action consumers are expected to take after they have heard and understood the toll-free statement.

Response: The purpose of this research is not to determine what action consumers will take after seeing the ad. We addressed these issues in the previous study, referenced on page 5 of this document. The purpose of the current proposed study is to determine whether the risk information is adequately comprehended and whether the toll-free statement is noticeable and recalled.

• What are the thresholds for interference ("detraction") in this study? Specifically, will the statement be included only if it does not affect risk comprehension at all, or if it does not affect risk comprehension "much"—and if this is the case, what is too much?

Response: Please see the answer to a similar question by sanofi-aventis, located on page 14 of this document.

External Reviewers

As requested by Congress, the Agency consulted with the Risk Communications Advisory Committee in May of 2008. Please see section A1 (*Circumstances Making the Collection of Information Necessary*, p. 3) for more detail. This extensive and public vetting resulted in a stronger and sharper research endeavor.

9. Explanation of Any Payment or Gift to Respondents

Internet panel participants are enrolled into a points program that is analogous to a 'frequent flyer' card in that respondents are credited with points in proportion to their regular participation in surveys (for the households provided internet appliances and an internet connection, their incentive is the hardware and internet service). Panelists receive cash-equivalent checks approximately every four to six months in amounts reflecting their level of participation in the panel, which commonly results in distributions in the range of $4 to $6 per month. Because this survey will take a little extra time to complete, participants will receive a survey-specific incentive equivalent to $5. The incentive will be paid in points that can be converted into sweepstakes entries or cash.

10. Assurance of Confidentiality Provided to Respondents

All respondents will be provided with the assurance of confidentiality. The experimental instructions will include information explaining to respondents that their information will be kept confidential.

No personally identifiable information will be sent to FDA. All information that can identify individual respondents will be kept by the independent contractor in a form that is

separate from the data provided to FDA. The information will be kept in a secured fashion that will not permit unauthorized access. These methods will all be approved by FDA's Institutional Review Board (Research Involving Human Subjects Committee, RIHSC) prior to collecting any information.

All electronic data will be maintained in a manner consistent with the Department of Health and Human Services' ADP Systems Security Policy as described in the DHHS ADP Systems Manual, Part 6, chapters 6-30 and 6-35. All data will also be maintained in consistency with the FDA Privacy Act System of Records #09-10-0009 (Special Studies and Surveys on FDA Regulated Products).

11. Justification for Sensitive Questions

This data collection will not include sensitive questions. The complete list of questions is available in Attachment 2.

12. Estimates of Annualized Burden Hours and Costs

The total annual estimated burden imposed by this collection of information is 2,774 hours for this one-time collection (Table 1).

Table 1. Estimated Annual Reporting Burden[a]

Activity	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
Screener, pretesing	2,800	1	2,800	.03	84
Questionnaire, pretesting	1,400	1	1,400	.25	350
Screener, study	12,000	1	12,000	.03	360
Questionnaire, study	6,000	1	6,000	.33	1,980

Total					2,774

[a]There are no capital costs or operating and maintenance costs associated with this collection of information.

These estimates are based on FDA's experience with previous consumer studies.

13. Estimates of Other Total Annual Costs to Respondents and Record Keepers

There are no costs to respondents. There are no record keepers.

14. Annualized Cost to the Federal Government

The estimated cost to the Federal Government for the collection of pretest and main study data is $850,000. This includes the costs paid to the contractors to create stimuli, to program the study, draw the sample, collect the data, and create a database of the results. The cost also includes FDA and DHHS staff time to design and manage the study, to analyze the resultant data, and to draft a report.

15. Explanation for Programs Changes or Adjustments

This is a new data collection.

16. Plans for Tabulation and Publication and Project Time Schedule

Conventional statistical techniques for experimental data, such as descriptive statistics, analysis of variance, and regression models, will be used to analyze the data. The Agency anticipates disseminating the results of the study after the final analyses of the data are completed, reviewed, and cleared. The exact timing and nature of any such dissemination has not been determined, but may include presentations and articles at trade and academic conferences, publications, and Internet posting.

Project Timetable

Task	Estimated Completion Date
External Peer Review	May, 2008

RIHSC Review	June, 2009
30-day FR notice publication	June, 2009
OMB Review of PRA package	July, 2009
Pretesting	August, 2009
Data Collection	October, 2009
Receipt of Data and Methods Report from Contractor	November, 2009
Data Analysis	December, 2009
Draft Report	January, 2010
Internal Review of Draft Report	February, 2010
Revisions	March, 2010
Final Report	April, 2010

17. Reason(s) Display of OMB Expiration Date is Inappropriate

No exemption is requested.

18. Exceptions to Certification for Paperwork Reduction Act Submissions

No exceptions are requested.

B. COLLECTIONS OF INFORMATION EMPLOYING STATISTICAL METHODS

1. Respondent Universe and Sampling Methods

The universe for this experimental study is members of the Knowledge Networks Internet panel. Knowledge Network's Internet panel consists of 50,000 adult panel members who are recruited by random-digit dialing (RDD) or by using address-based sampling. The sample is nationally representative and statistically accurate. Typical panel members receive 3-4 invitations per month to participate in research projects.

The 1,500 participants for this study would be drawn from the pool of over 43,000 panel members. Quotas will be used so that the overall sample is in proportion to the U.S. adult population on gender and race/ethnicity. A range of participants over the age of 30 will be selected to approximate a reasonable sample of individuals for whom high blood pressure may be a concern. At least 20% of the sample will have achieved a high school education or less.

FDA does not intend to generate nationally or locally representative results or precise estimates of population parameters from this study. The sample used is a convenience sample, rather than a probability sample. Despite the attempt to match between the study's sample and known population characteristics, matching is used solely to produce samples with a reasonable degree of diversity in key demographic characteristics. Furthermore, no legitimate weights can be constructed from non-probability samples such as the one used here. Hence, the Agency does not construe this sample or the results generated from this sample as nationally or locally representative. Rather, the strength of the experimental study lies in its internal validity, on which meaningful estimates of differences across conditions can be produced and generalized.

Overview

This study will examine the placement of the toll-free statement and the length of time the statement is presented on-screen in a DTC television advertisement for a prescription drug. The primary dependent measure of interest is consumer comprehension of the important risk information in the advertisement. This study will also examine potential differences in comprehension based on the wording of the toll-free statement and the prominence of the statement.

The application of a new piece of information for viewers of DTC ads presents logistical challenges. From a research perspective, the primary issue under investigation is how to impart additional information without increasing "cognitive load," thus leading to information overload. Cognitive load is an index of the memory demands necessary to process a set of information.[4] As cognitive load increases, more mental resources are necessary to process and understand the information. DTC ads are already quite dense when compared to ads for other products. The risk information in the major statement of the ad should not be compromised by the addition of the toll-free statement. At the same time, it is preferable that the risk information and the toll-free statement information are presented in such a way that both are understandable. We have chosen a set of variables in the current study to investigate issues of cognitive load. They are described briefly below before examining the details of the research design.

1. Placement

The location of the toll-free statement may facilitate or detract from the risk information in the major statement. We have chosen three locations for this information to test

[4] Chandler, P. and Sweller, J. (1991). Cognitive load theory and the format of instruction. *Cognition and Instruction*, *8*(4), 293-332.

which location results in the greatest communication of the risks of the drug and the concept that side effects can be reported. It is possible that locating the toll-free statement before the major statement provides a "prime" for the risk information that follows; that is, the mention of side effects in the toll-free statement will cause consumers to start thinking about side effect-related information, which facilitates comprehension of the risk information that follows. In this case, the two conceptual pieces of information may flow together easily. Conversely, it is possible that the toll-free statement confuses consumers or provides no information for them because they have not yet heard any risk information. Thus, without context, the statement lacks applicability.

Placing the toll-free statement during the major statement likely reduces the comprehension of the risk information for the drug because it divides viewer's attention between two competing pieces of information. It is possible, however, that the juxtaposition of these two informational concepts are complimentary and therefore do not conflict.

The toll-free statement may serve the best role after the risk information has been presented. In this case, participants have been told about the risks and side effects of the drug before they are told they may report this information. This essentially primes the toll-free statement with the major statement. We do not expect this placement to interfere with the comprehension of risk information, as it is not present during the voicing of risks and has not been introduced to viewers at this point. In addition, the usefulness of the toll-free statement may improve in this condition relative to those discussed above because viewers have been provided with context.

Over time, it is likely that the toll-free statement will become part of the background of the ads as people become accustomed to seeing this statement in all DTC ads. In this respect, people will have the statement as an option if needed but will be able to disregard it to focus on

the risk information when desired. Thus, we are testing a condition in which the toll-free statement will be present during the entire ad. This test condition will control for the effect of novelty arising from the fact that consumers have not previously seen this type of statement in TV ads. Presence of the statement during the entire ad may increase noticeability of the toll-free statement initially, but will be unlikely to interfere with risk information in the long run.

2. Statement wording

The second variable, *statement type*, will have two executions of statement language: the language from the FDAAA versus the language used in the final *Toll-Free Number for Reporting Adverse Events on Labeling for Human Drug Products* Rule (TFNR) and previously tested by FDA. The wording from these two statements is as follows:

1. "You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088." (*FDAAA*)

2. "Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088 or www.fda.gov/medwatch." (*TFNR)*

We think it is important to test both the toll-free statement version in FDAAA and the version that we have previously tested with actual consumers. The most obvious reason for this is to make sure that the statement is maximally readable and understandable. It may be valuable, however, to test two statements for another reason.

If the toll-free statement is enacted in broadcast ads, it is possible that because of the boilerplate language, some amount of habituation will occur. That is, after viewers have seen the same language in multiple ads for multiple products, they may "tune out" and not pay attention to the toll-free statement at all. If we test two versions of the statement and find both acceptable, it would be possible to either allow sponsors to choose one statement versus another or to

suggest some alternating of the two statements. This is a long-term idea, however, and finding appropriate wording is the primary goal of investigating this variable.

3. Duration

Congress specifically mandates that we investigate the duration of the display of the toll-free statement. As with placement, the length of time the toll-free statement is presented on-screen may influence the cognitive load in the ad. For experimental control, we will look at the duration of the statement while holding placement in the ad (after the major statement of risks) constant. Although this placement should not interfere with the processing of the risk information, it is possible that the duration influences the take away message from the ad. For example, having the statement on for a short amount of time may not give consumers enough time to read and process the message, resulting in lower comprehension of the message but have no impact on the comprehension of the risk information. Alternatively, displaying the toll-free statement for a longer period of time may wipe away memory traces of the risks from the major statement, resulting in lower risk comprehension. Whether this longer duration increases the usefulness of the toll-free statement itself is an empirical question. We will compare these short and long durations to instances where the toll-free statement is present during the entire ad and when there is no toll-free statement at all.

4. Prominence

In addition to superimposing the toll-free statement on the screen during the ad, there are other methods available to increase the prominence of the statement. In particular, having the statement read aloud in the ad voiceover while the statement is on the screen may be considered particularly prominent. Does the additional prominence of the statement compromise the comprehension of the risk information in the major statement? If not, does the additional

prominence result in a greater understanding of the toll-free statement itself? It is likely that there is a tradeoff between the gains of emphasizing the toll-free statement and the comprehension of the risk information, given the limited cognitive capacity of viewers. In examining this variable, we are exploring the parameters of this tradeoff.

Design

The design will consist of three parts. Part one will be a between-subjects factorial design examining the placement of the toll-free statement by the type of statement. The first variable, *placement*, will have four levels: before the major statement of risks, during the major statement of risks, after the major statement of risks, or continuously throughout the whole ad.

In each condition the toll-free statement will appear in the ad as superimposed text at the bottom of the screen. We will also include a control condition in which the statement does not appear.

Part One: Placement by Statement Type
4 x 2 + 1

	Statement Type	
Placement	FDAAA	TFNR
Before major statement of risks		
During major statement of risks		
After major statement of risks		
During the whole ad		

Plus:

Control (no toll-free statement)

Part two of the study will examine four variations in the duration of the toll-free statement using the language from the FDAAA: short (on screen for approximately 3 seconds after the major statement), long (on screen for approximately 6 seconds after the major

statement), on screen during the whole ad, and the control condition of no toll-free statement included. These times were adopted by calculating how long it would take a person reading at an average reading speed to read the statement. As in the first part of this study series, the toll-free statement will appear as superimposed text and a control condition in which the toll-free statement does not appear will be included.

Part Two: Duration*
4 x 1

Short (On screen for approximately 3 seconds after major statement)
Long (On screen for approximately 6 seconds after major statement)
During the Whole Ad
Control (no toll-free statement)

*Using FDAAA statement

Part three of the study will examine two variations in the prominence of the toll-free statement using the language from the FDAAA: Spoken after the major statement with only the website and phone number in superimposed text, and a control condition where the toll-free statement is presented visually after the major statement.

Part Three: Prominence*
2 x 1

Extra Prominent (spoken after major statement of risks, website and phone number on screen)
Control (after major statement of risks)

*Using FDAAA statement

We will investigate these issues in one disease condition, high blood pressure, because high blood pressure has a high incidence rate in the population, is a public health concern, and is likely to occur in both males and females. Further, because there is little broadcast promotion for

prescription treatment of high blood pressure at this time, participants should be less familiar with DTC television ads for this type of drug, reducing the potential influence of prior experience.

Our primary dependent variable is comprehension of the risk information mentioned in the major statement. In addition to this variable, we will also examine comprehension of benefit information. We will also examine the noticeability and comprehension of the toll-free statement.

Procedure

Participants will see an advertising pod of four ads: two 15-second non-DTC ads (fillers), an approximately 60-second DTC ad for a fictitious high blood pressure medication, and a 30-second DTC ad for an unrelated medical condition with the same toll-free statement included. We include two DTC ads with the toll-free statement in our protocol because this better approximates what will happen if this statement is enacted. That is, viewers will see the statement in all DTC ads for all products. In this study, we want to avoid the suggestion that there is something particular about the high blood pressure drug class that causes the statement to be mandated. Thus, we will show multiple DTC ads but ask questions regarding only the ad which has been manipulated to test our hypotheses. To maximize response information, the test ad will always be the last ad they see.

After viewing the ads, a structured interview will be conducted. Participants will answer questions about the high blood pressure DTC test ad they have seen. Questions will examine a number of important perceptions about the advertised product, including risk comprehension, risk recall, benefit comprehension, benefit recall, behavioral intention, noticeability of the toll-free statement, and recall of the toll-free statement.

Finally, demographic and health care utilization information will be collected. The entire procedure is expected to last approximately 20 minutes. A total of 6,000 interviews will be completed. This will be a one-time (rather than annual) information collection.

Participants

Data will be collected using an Internet protocol. Two samples of consumers will be recruited: one sample of individuals diagnosed with high blood pressure and another sample of consumers over the age of 21. Both groups will represent a range of education levels. Because the task presumes basic reading abilities, all selected participants must speak English as their primary language.

FDA proposes to conduct two rounds of pretesting with 700 consumers in each round to refine the questionnaire and the stimuli before fielding the main study.

Hypotheses

Overall, we expect effects to be stronger in the high blood pressure sample than in the general population sample, as high blood pressure sufferers will likely have higher involvement with the medical condition.

Risk Comprehension

• Any inclusion of the toll-free statement will reduce the comprehension of risk information.
(Risk comprehension will be highest in control condition for all analyses)

• Placement:

-Conditions in which the statement is presented after the major statement and the statement is present for the whole ad will reduce comprehension least.
(After control condition, risk comprehension will be highest in conditions where statement is present for whole ad or after the major statement; risk comprehension will be lowest when statement is presented during or before the major statement).

• Wording: Type of statement will not influence risk comprehension.

• Placement x Wording: This analysis is exploratory

• Duration:

-Statement will interfere with risk comprehension less when presented in the whole ad than when presented for briefer periods.

-Short duration will result in lower risk comprehension than long duration because it will be displayed for a short time, causing attention to shift twice in quick succession

(Risk comprehension highest in control condition, followed by whole ad condition followed by long duration, and, finally, short duration)

• Prominence: Prominence of statement will not affect risk comprehension.

Benefit Comprehension

• Any inclusion of the toll-free statement will reduce the comprehension of benefit information.

(Benefit comprehension will be highest in control condition for all analyses)

• Placement:

-Conditions in which the statement is presented after the major statement and the statement is present for the whole ad will reduce comprehension least.

(After control condition, benefit comprehension will be highest in conditions where statement is present for whole ad or after the major statement; benefit comprehension will be lowest when statement is presented during or before the major statement).

• Wording: Type of statement will not influence benefit comprehension.

• Placement x Wording: This analysis is exploratory

• Duration:

-Statement will interfere with benefit comprehension most when presented in the whole ad than when presented for briefer periods after the major statement.

-No prediction of differences between short and long duration of statement on benefit comprehension.

(Benefit comprehension highest in control condition, followed short and long duration conditions together, followed by condition where statement is present in whole ad)

• Prominence: Prominence of statement will not affect benefit comprehension.

Toll-Free Statement Recall

• Toll-free statement recall will be higher in any condition where it is included in the ad.

• Placement:

-Recall of statement will be highest in conditions where it is on screen for the whole ad and where it is placed after the major statement.

• Wording: This analysis is exploratory.

• Placement x Wording: This analysis is exploratory

• Duration:
-Recall of the statement will be greatest in the condition where it is present for the whole ad, followed by the condition in which it is located after the major statement.

• Prominence:
-Recall of the statement will be higher in the Extra Prominent condition than in the condition in which it is only in super form after the major statement

Behavioral Intention

• This analysis is exploratory and for completeness.

Power

The following assumptions were made in deriving the sample size: (1) 0.05 alpha and 0.90 power and (2) an effect size between small and medium. The table below presents the per group sample sizes needed to detect differences with effect sizes ranging from conventionally "small" (f=.1) to "medium" (f=.25) across the different designs utilized in this study (see Cohen, 1988, Table 8.4.4, "n to detect f by F test at a = .05"; p. 384).[5] Thus, based on these assumptions, a per group sample size of 250 should provide adequate power to detect smallish to medium effect sizes across our designs.

Per group sample size required, by effect size (f) and design, with power = .90, alpha = .05.				
	f=.1	f=.15	f=.2	f=.25
5X1 ANOVA	309	138	78	50
4X1 ANOVA	354	158	89	58
2X1 ANOVA	526	234	132	68

Analysis Plan

[5] Cohen, Jacob (1988). Statistical Power Analysis for the Behavioral Sciences, Second Edition. Hillsdale, NJ: Lawrence Erlbaum Associates.

We will conduct the following analyses separately for the general population sample and the high blood pressure sufferers sample. Once these separate analyses are completed, we will conduct the analyses with the samples combined, using the type of sample as a moderator variable to determine whether any effects differed significantly between the groups.

Part 1: We will test whether there is a main effect of placement on our main dependent variables (i.e., risk comprehension, benefit comprehension, and behavioral intention) using one-way ANOVAs (4 placement conditions, plus control condition). We will conduct ANOVAs that assesses the main effect of placement (4 placement conditions), the main effect of statement type, and the interaction between placement and statement type on our main dependent variables. We will examine logistic regression models predicting toll-free statement recall from placement (4 placement conditions, plus control condition), and from placement, statement type, and the interaction between placement and statement type. We will conduct these analyses both with and without covariates (e.g., demographic and health characteristics) included in the model. In addition, we will test whether any main effects are moderated by other measured variables (e.g., time spent viewing the ad, demographic and health characteristics). If any main effects are significant, we will conduct pairwise-comparisons to determine which conditions are significantly different from one another. We will also conduct planned comparisons in line with our hypotheses (see above).

Part 2: We will test whether there is a main effect of duration on our main dependent variables using one-way ANOVAs and logistic regression models. We will examine these analyses both with and without covariates (e.g., demographic and health characteristics) included in the model. In addition, we will test whether the main effect is moderated by other measured variables (e.g., time spent viewing the ad, demographic and health characteristics). If the main

effect is significant, we will conduct pairwise-comparisons to determine which conditions are significantly different from one another. We will also conduct planned comparisons in line with our hypotheses (see above).

Part 3: We will test whether there is a main effect of prominence on our main dependent variables using one-way ANOVAs and logistic regression models. We will examine these analyses both with and without covariates (e.g., demographic and health characteristics) included in the model. In addition, we will test whether the main effect is moderated by other measured variables (e.g., time spent viewing the ad, demographic and health characteristics).

Pretesting of Stimuli

Key to our study is the reasonableness and appropriateness of the stimuli we use to approximate television DTC prescription drug ads. Because the particular images are subjective, we will conduct extensive pretesting with consumers similar to our main target audience. This pretesting will involve 700 individuals in two waves. The purpose of the pretesting is to ensure that the stimuli are perceived as realistic. During the pretesting stage, the primary dependent variable will be the success of the particular manipulation. The pretesting will allow us to make changes in the ad stimuli before the actual study commences, thus making participants' time more valuable.

2. <u>Procedures for the Collection of Information</u>

Respondents will participate in the study via the Internet (see sampling criteria above). They will watch an advertising pod consisting of four advertisements, including one non-test DTC ad, two filler ads for non-pharmaceutical products, and the test ad, always placed last in the series. The non-test ad will have a similar presentation of the toll-free statement to ensure that consumers do not think there is something particular about the stimulus product that would

require a special statement. Participants will then answer questions, as shown in Attachment 2. The whole procedure will take no more than 20 minutes.

3. Methods to Maximize Response Rates and to Deal with Issues of Non-Response

This experimental study will use an existing Internet panel to draw a sample. The panel includes people who have expressed interest in sharing their opinions via the Internet and do so regularly. The expected participation rate for the Internet panel is 55 percent when responding to a specific study. To help ensure that the participation rate is as high as possible, FDA will:

- Design an experimental protocol that minimizes burden (short in length, clearly written, and with appealing graphics);
- Administer the experiment over the Internet, allowing respondents to answer questions at a time and location of their choosing;
- Administer the experiment to individuals who have expressed interest in participating in Internet studies;
- Email a reminder to the respondents who do not complete the protocol four days after the original invitation to participate is sent;
- Provide contact information on where to get help for respondents who may have questions as they complete the experiment.

4. Test Procedures

The contractor will run nine participants through the procedure to assess questionnaire wording, basic glitches in the programming and execution of the study. This pretest is designed to ensure that questionnaire wording is clear and that procedures for viewing stimuli and proceeding through the experiment are as planned. The stimuli will be tested in two waves of 700 participants to ensure that the stimuli are perceived as realistic.

5. Individuals Involved in Statistical Consultation and Information Collection

The contractor, RTI International, will collect the information on behalf of FDA as a task order under the Quick-Turn-Around Research Services contract. Claudia Squire, Ph.D., is the Project Director for this project, telephone (919) 541-6613. Data analysis will be conducted primarily by the Research Team, Division of Drug Marketing, Advertising, and Communications (DDMAC), Office of Medical Policy, CDER, FDA, and coordinated by Kathryn J. Aikin, Ph.D., 301-796-0569 and Amie C. O'Donoghue, Ph.D., 301-796-0574.

ATTACHMENT 1

[Federal Register: November 26, 2008 (Volume 73, Number 229)]
[Notices]
[Page 72058-72062]
From the Federal Register Online via GPO Access [wais.access.gpo.gov]
[DOCID:fr26no08-83]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2008-N-0595]

Agency Information Collection Activities; Proposed Collection; Comment Request; Experimental Study: Toll-Free Number for Consumer Reporting of Drug Product Side Effects in Direct-to-Consumer Television Advertisements for Prescription Drugs

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing an opportunity for public comment on a proposed collection of certain information by the agency. Under the Paperwork Reduction Act of 1995 (the PRA), Federal agencies are required to publish notice in the Federal Register concerning each proposed collection of information, including each proposed extension of an existing collection of information, and to allow 60 days for public comment in response to the notice. This notice solicits comments on a study examining the impact on consumer comprehension of inclusion of a toll-free number to report side effects in direct-to-consumer (DTC) prescription drug television advertisements.

DATES: Submit written or electronic comments on the collection of information by January 26, 2009.

ADDRESSES: Submit electronic comments on the collection of information to http://www.regulations.gov. Submit written comments on the collection of information to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT: Elizabeth Berbakos,Office of Information Management (HFA-710), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-796-3792.

SUPPLEMENTARY INFORMATION: Under the PRA (44 U.S.C. 3501-3520), Federal agencies must obtain approval from the Office of Management and Budget

(OMB) for each collection of information they conduct or sponsor. ``Collection of information'' is defined in 44 U.S.C. 3502(3) and 5 CFR 1320.3(c) and includes agency requests or requirements that members of the public submit reports, keep records, or provide information to a third party. Section 3506(c)(2)(A) of the PRA (44 U.S.C. 3506(c)(2)(A)) requires Federal agencies to provide a 60-day notice in the Federal Register concerning each proposed collection of information, including each proposed extension of an existing collection of information, before submitting the collection to OMB for approval. To comply with this requirement, FDA is publishing notice of the proposed collection of information set forth in this document.

With respect to the following collection of information, FDA invites comments on these topics: (1) whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Toll-Free Number for Consumer Reporting of Drug Product Side Effects in Direct-to-Consumer Television Advertisements for Prescription Drugs

The Federal Food, Drug, and Cosmetic Act (the act) requires that manufacturers, packers, and distributors (sponsors) who advertise prescription human and animal drugs, including biological products for humans, disclose in advertisements certain information about the advertised product's uses and risks. For prescription drugs and biologics, the act requires advertisements to contain ``information in brief summary relating to side effects, contraindications, and effectiveness'' (21 U.S.C. 352(n)). FDA is responsible for enforcing the act and implementing regulations.

On September 27, 2007, the President signed into law the Food and Drug Administration Amendments Act (FDAAA) (Public Law 110-85). Title IX of FDAAA amends section 502(n) of the act (21 U.S.C. 352) by requiring printed DTC advertisements for prescription drug products to include the following statement printed in conspicuous text: ``You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.'' Title IX of FDAAA also requires the Secretary of Health and Human Services (the Secretary), in consultation with the Risk Communication Advisory Committee (RCAC), to conduct a study not later than 6 months after the date of enactment of FDAAA to determine if this statement is appropriate for inclusion in DTC television advertisements for prescription drug products. As part of this study, the Secretary shall consider whether the information in the statement described previously in this paragraph would

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detract from the presentation of risk information in a DTC television advertisement. If the Secretary determines that the inclusion of such a statement would be appropriate for television advertisements, FDAAA mandates the issuance of regulations implementing this requirement, and

for the regulations to reflect a reasonable length of time for displaying the statement in television advertisements. Finally, FDAAA requires the Secretary to report the study's findings and any subsequent plans to issue regulations to Congress.

In accordance with the requirements of FDAAA, FDA convened a meeting of the RCAC on May 15 and 16, 2008. A draft design for studying this issue was proposed at that time and discussed by the Advisory Committee. Based on comments received at that meeting, changes were made to the proposed study design. The transcripts and materials from that meeting can be found online at http://www.fda.gov/ohrms/dockets/ac/oc08.html#RCAC.

Relevant Prior History and Research

Section 17 of the Best Pharmaceuticals for Children Act (the BPCA) (Public Law 107-109, January 4, 2002) required FDA to issue a final rule mandating the addition of a statement to the labeling of each drug product for which an application is approved under section 505 of the act (21 U.S.C. 355). Under the BPCA, the statements must include: (1) A toll-free number maintained by FDA for the purpose of receiving reports of adverse events regarding drugs; and (2) a statement that the number is to be used only for reporting purposes, and it should not be used to seek or obtain medical advice (the side effects statement).

On April 22, 2004, FDA published a proposed rule with a proposed side effects statement for certain prescription drug product labeling and a proposed side effects statement for certain over-the-counter drug product labeling (69 FR 21778). In the proposed rule, FDA solicited comments on a proposed statement that FDA believed comported with the previously mentioned mandate in the BPCA. The agency received 12 comments suggesting changes to the specific wording proposed. The agency also received several comments suggesting that FDA engage in research to study the wording of the proposed side effects statement with consumers. Among the reasons cited for testing the statement were to: (1) Determine the best and most precise wording for the statement, (2) evaluate consumer comprehension of the proposed statement, and (3) address concerns that consumers who read the statement will mistakenly call FDA in search of medical advice rather than seeking appropriate medical treatment. In addition, during the clearance process for the proposed rule, both the Office of Information and Regulatory Affairs of OMB and the Office of the Assistant Secretary for Planning and Evaluation of the Department of Health and Human Services suggested that FDA conduct focus groups or other consumer studies to inform the wording of the side effects statement.

During the spring of 2006, to assist in developing this study, FDA conducted two focus groups to gauge consumer understanding and preferences for a number of proposed side effects statements and to narrow the number of statements to be tested in subsequent experimental research. In addition to the information collected on which versions of the statements participants preferred, discussions showed that people varied in their understanding of when to call FDA or their health care practitioners and that some people would not call FDA even if they experienced a serious side effect. Several people in the focus groups suggested the addition of a Web site to report adverse side effects.

Based on the findings from the focus groups, nine statements were selected for quantitative testing. A labeling comprehension experiment was conducted with 1,674 men and women ranging in age from 21 to 95 with varying levels of education (OMB Control No. 0910-0497). The results from that quantitative test found that only one of the versions tested was rated as significantly less clear than the others, which

were all rated as generally clear and understandable. The results also showed that participants reported they would not call FDA seeking medical advice. Further, among those participants who said they would call the FDA, the majority indicated they would call their doctor for medical advice, rather than FDA, regardless of the severity of the side effect. Finally, participants indicated they could distinguish between serious and non-serious side effects, reporting that they would seek emergency medical care in the case of serious side effects. The report of the study is available in the docket for the final rule, Docket No. FDA-2003-N-0313. The final rule, Toll-Free Number for Reporting Adverse Events on Labeling for Human Drug Products (TFNR) (73 FR 63886, October 28, 2008), is available online at http://www.fda.gov/OHRMS/DOCKETS/98fr/E8-25670.pdf.

Proposed Research

This study will examine the placement of the toll-free statement and the length of time the statement is presented on-screen in a DTC television advertisement for a prescription drug. The primary dependent measure of interest is consumer comprehension of the risk information in the advertisement. This study will also examine potential differences in comprehension based on the wording of the toll-free statement and the prominence of the statement.

The application of a new piece of information for viewers of DTC ads presents logistical challenges. From a research perspective, the primary issue under investigation is how to impart additional information without increasing ``cognitive load,'' thus leading to information overload. Cognitive load is an index of the memory demands necessary to process a set of information. As cognitive load increases, more mental resources are necessary to process and understand the information.\1\ DTC ads are already quite dense when compared to ads for other products. The risk information in the major statement of the ad should not be compromised by the addition of the toll-free statement. At the same time, it is preferable that the risk information and the toll-free statement information are presented in such a way that both are understandable. We have chosen a set of variables in the current study to investigate issues of cognitive load. They are described briefly in the following paragraphs before examining the details of the research design.

\1\ Chandler, P. and J. Sweller, ``Cognitive Load Theory and the Format of Instruction.'' Cognition and Instruction, 8(4), 293-332, 1991.

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1. Placement

The location of the toll-free statement may facilitate or detract from the risk information in the major statement. We have chosen three locations for this information to test which location results in the greatest communication of the risks of the drug and the concept that side effects can be reported. It is possible that locating the toll-free statement before the major statement provides a ``prime'' for the risk information that follows; that is, the mention of side effects in the toll-free statement will cause consumers to start thinking about side effect-related information, which facilitates comprehension of the risk information that follows. In this case, the two conceptual pieces of information may flow together easily. Conversely, it is possible

that locating the toll-free statement here confuses consumers or provides no information for them

[[Page 72060]]

because they have not yet heard any risk information. Thus, without context, the statement lacks applicability.

Placing the toll-free statement during the major statement likely reduces the comprehension of the risk information for the drug because it divides viewer's attention between two competing pieces of information. It is possible, however, that the juxtaposition of these two informational concepts are complimentary and therefore do not conflict.

The toll-free statement may serve the best role if it is located after the risk information has been presented. In this case, participants have been told about the risks and side effects of the drug before they are told they may report this information. This essentially primes the toll-free statement with the major statement. We do not expect this placement to interfere with the comprehension of risk information, as it is not present during the voicing of risks and has not been introduced to viewers at this point. The usefulness of the toll-free statement, however, may improve in this condition relative to those discussed above because viewers have been provided with context.

Over time, it is likely that the toll-free statement will become part of the background of the ads as people become accustomed to seeing this statement in all DTC ads. In this respect, people will have the statement as an option if needed but will be able to disregard it to focus on the risk information when desired. Thus, we are testing a condition in which the toll-free statement will be present during the entire ad. This test condition will control for the effect of novelty arising from the fact that consumers have not previously seen this type of statement in TV ads. Presence of the statement during the entire ad may increase noticeability of the toll-free statement initially, but will be unlikely to interfere with risk information in the long run.

2. Statement Wording

The second variable, statement type, will have two executions of statement language: The language from FDAAA versus the language used in the TFNR and previously tested by FDA. The wording from these two statements is as follows:

``You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.'' (FDAAA)

``Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.'' (TFNR)

We think it is important to test both the toll-free statement version in FDAAA and the version that we have previously tested with actual consumers. The most obvious reason for this is to make sure that the statement is maximally readable and understandable. It may be valuable, however, to test two statements for another reason.

If the toll-free statement is enacted in broadcast ads, it is possible that because of the boilerplate language, some amount of ``burnout'' will occur. That is, after viewers have seen the same language in multiple ads for multiple products, they may ``tune out'' and not pay attention to the toll-free statement at all. If we test two versions of the statement and find both acceptable, it would be possible to either allow sponsors to choose one statement versus

another or to suggest some alternating of the two statements. This is a long-term idea, however, and finding appropriate wording is the primary goal of investigating this variable.

3. Duration

Congress specifically mandates that we investigate the duration of the display of the toll-free statement. As with placement, the length of time the toll-free statement is presented on-screen may influence the cognitive load in the ad. For experimental control, we will look at the duration of the statement while holding placement in the ad (after the major statement of risks) constant. Although this placement should not interfere with the processing of the risk information, it is possible that the duration influences the take away message from the ad. For example, having the statement on for a short amount of time may not give consumers enough time to read and process the message, resulting in lower comprehension of the message but no impact on the comprehension of the risk information. Alternatively, displaying the toll-free statement for a longer period of time may wipe away memory traces of the risks from the major statement, resulting in lower risk comprehension. Whether this longer duration increases the usefulness of the toll-free statement itself is an empirical question. We will compare these short and long durations to instances where the toll-free statement is present during the entire ad and where there is no toll-free statement at all.

4. Prominence

In addition to superimposing the toll-free statement on the screen during the ad, there are other methods available to increase the prominence of the statement. In particular, having the statement read aloud in the ad voiceover while the statement is on the screen may be considered particularly prominent. Does the additional prominence of the statement compromise the comprehension of the risk information in the major statement? If not, does the additional prominence result in a greater understanding of the toll-free statement itself? It is likely that there is a tradeoff between the gains of emphasizing the toll-free statement and the comprehension of the risk information, given the limited cognitive capacity of viewers. In examining this variable, we are exploring the parameters of this tradeoff.

Design Overview

The design will consist of three parts. Part one will be a between-subjects factorial design examining the placement of the toll-free statement by the type of statement. The first variable, placement, will have four levels: (1) Before the major statement of risks, (2) during the major statement of risks, (3) after the major statement of risks, or (4) continuously throughout the whole ad.

In each condition the toll-free statement will appear in the ad as superimposed text at the bottom of the screen. We will also include a control condition in which the statement does not appear.

Part One: Placement by Statement Type
4 x 2 + 1

	Statement Type	
Placement	FDAAA	TFNR
Before major statement of risks	.....	.....

During major statement of risks ....

[[Page 72061]]

After major statement of risks ....

During the whole ad ....

Plus:

Control (no toll-free statement)

Part two of the study will examine four variations in the duration of the toll-free statement using the language from FDAAA: (1) Short (approximately 3 seconds after the major statement), (2) long (approximately 6 seconds after the major statement), (3) during the whole ad, and (4) the control condition of no toll-free statement included. These times were adopted by calculating how long it would take a person reading at an average reading speed to read the statement. As in the first part of this study series, the toll-free statement will appear as superimposed text and a control condition in which the toll-free statement does not appear will be included.

Part Two: Duration*\
4 x 1

Short (Approximately 3 seconds)

Long (Approximately 6 seconds)

During the whole ad

Control (no toll-free statement)

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*\Using FDAAA statement

Part three of the study will examine two variations in the prominence of the toll-free statement using the language from FDAAA: Spoken with only the Web site and telephone number in superimposed text; or spoken with the full statement superimposed in text. Both variants in part three will place the toll-free statement after the major statement of risks. There will also be a control condition in which the statement does not appear at all.

Part Three: Prominence*\ 3 x 1
Audio Only (spoken after major statement of risks, website and phone number on screen)
Extra Prominent (spoken after major statement of risks, entire toll-free statement on screen)
Control (no toll-free statement)

*\Using FDAAA statement

We will investigate these issues in one disease condition, high blood pressure, because high blood pressure has a high incidence rate in the population, is a public health concern, and is likely to occur in both males and females. Further, because there is little promotion for prescription treatment of high blood pressure, participants should be less familiar with DTC television ads for this type of drug, reducing the potential influence of prior experience.

Our primary dependent variable is comprehension of the risk information mentioned in the major statement. In addition to this variable, we will also examine comprehension of benefit information. We will also examine the noticeability and comprehension of the toll-free statement.

Procedure

Participants will see an advertising pod of four ads: Two non-DTC ads (fillers), a DTC ad for a fictitious high blood pressure medication, and a DTC ad for an unrelated medical condition with the same toll-free statement included. We include two DTC ads with the toll-free statement in our protocol because this better approximates what will happen if this statement is required to be implemented in DTC TV ads. That

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is, viewers will see the statement in all DTC ads for all products. In this study, we want to avoid the suggestion that there is something particular about the high blood pressure drug class that causes the statement to be mandated. Thus, we will show multiple DTC ads but ask questions regarding only the ad which has been manipulated to test our hypotheses. To maximize response information, the test ad will always be the last ad participants see.

After viewing the ads, a structured interview will be conducted. Participants will answer questions about the high blood pressure DTC test ad they have seen. Questions will examine a number of important perceptions about the advertised product, including risk comprehension, risk recall, benefit comprehension, benefit recall, behavioral intention, noticeability of the toll-free statement, and comprehension of the toll-free statement.

Finally, demographic and health care utilization information will be collected. The entire procedure is expected to last approximately 15 minutes. A total of 1,600 interviews will be completed. This will be a one-time (rather than annual) information collection.

Participants

Data will be collected using an Internet protocol. Consumers over the age of 18 will be screened and recruited by the contractor to represent a range of education levels. Because the task presumes basic

reading abilities, all selected participants must speak English as their primary language.

FDA proposes to conduct 2 rounds of pretesting with 200 consumers in each round to refine the questionnaire and the stimuli before fielding the main study.

FDA estimates the burden of this collection of information as follows:

FDA estimates that 2,400 individuals will need to be screened to obtain a respondent sample of 400 for the pretests and 1,600 for the study. The screener is expected to take 30 seconds, for a total screener burden of 20 hours. The ad viewing and questionnaire are expected to take 15 minutes for the participants in the pretest and the main study, for a cumulative study burden of 500 hours. The estimated total burden for this data collection effort is 520 hours. The respondent burden is provided in table 1 of this document:

Table 1--Estimated Annual Reporting Burden \1\

No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
2,400 (screener)	1	2,400	.008	20
400 (pretest)	1	400	.25	100
1,600 (study)	1	1,600	.25	400
Total				520

\1\ There are no capital costs or operating and maintenance costs associated with this collection of information.

Please note that on January 15, 2008, the FDA Division of Dockets Management Web site transitioned to the Federal Dockets Management System (FDMS). FDMS is a Government-wide, electronic docket management system. Electronic comments or submissions will be accepted by FDA only through FDMS at http://www.regulations.gov.

Dated: November 19, 2008.

Jeffrey Shuren,

Associate Commissioner for Policy and Planning.

[FR Doc. E8-28065 Filed 11-25-08; 8:45 am]

BILLING CODE 4160-01-S

ATTACHMENT 2

Questionnaire, Toll-Free 2 Study

Questionnaire will be administered via Internet.

• Informed consent procedures must be completed prior to beginning study
• Participants will be blind to FDA's sponsorship

Section I. Interview.

Thank you for agreeing to participate in this study today.

This study is about advertising for new products. You will see four ads and then answer questions about what you've seen. The study will take about 20 minutes.

[PROGRAMMER: Show ads in the following order:
1. 15-second non-DTC filler ad 1
2. 30-second unrelated DTC ad
3. 15-second non-DTC filler ad 2
4. ~60-second appropriate Zintria ad]

Now please answer the following questions.

Q1a. Do you recall seeing an ad for [unrelated DTC product]?

Yes
No
I'm not sure

Q1b. Do you recall seeing an ad for Zintria?

Yes
No [If "no," show participant Zintria ad only again and return them to questionnaire]
I'm not sure [If "not sure," show participant Zintria ad only again and return them to questionnaire]

Q2. How well do you think Zintria would or would not work for you?

Extremely Well
Quite Well
Moderately Well
Somewhat Well
Not Well At All

Q3. How safe or not safe do you think Zintria is?

Extremely Safe
Quite Safe
Moderately Safe
Somewhat Safe
Not at All Safe

Q4. How likely or not likely would you be to lower your blood pressure if you took Zintria?

Not at All Likely
Somewhat Likely
Moderately Likely
Quite Likely
Extremely Likely

Q5. How risky or not risky do you think Zintria is?

Not at all Risky
Somewhat Risky
Moderately Risky
Quite Risky
Extremely Risky

Q6. (Behavioral Intention) Please rate how likely or unlikely you are to do each of the following behaviors [PROGRAMMER: *randomize*]

	Very Likely	Somewhat Likely	Neither Likely nor Unlikely	Somewhat Unlikely	Very Unlikely
a. Talk to your doctor about Zintria					
b. Ask your doctor about getting a sample of Zintria					
c. Look for more information about Zintria					

d. Ask your doctor to prescribe Zintria					

Q7a. (Recall of risks) Answer these questions as best you can based on the information in the ad for Zintria.

[PROGRAMMER: *randomize*]

	True	False
a. Taking some kinds of over-the-counter cough medicines at the same time as taking Zintria increases your risk of having a heart attack.		
b. Zintria may cause excitability.		
c. If you have a very slow heart rate, you should not take Zintria.		
d. Zintria may cause you to have blurry vision.		
e. One of the most common side effects is tiredness.		
f. Antibiotics may not work as well if you use Zintria at the same time.		
g. You should have regular eye exams when you take Zintria.		
h. One of the most common side effects is nausea.		

Q7b. (Comprehension of risks)
Please choose a response based on the information in the ad.

[PROGRAMMER: *randomize items and item responses*]

i. Why should you NOT stop taking Zintria suddenly?

a. You may have unusual changes in behavior
b. Your eyes will have trouble adjusting to the change in pressure
c. You may have a temporary loss of coordination
d. You may experience chest pain

ii. When you first take Zintria, why should you avoid activities that require you to be alert?

a. You may have a temporary loss of coordination
b. A common side effect of Zintria is dizziness
c. A common side effect of Zintria is nervousness

d. You may faint

iii. Why might you have blurry vision when taking Zintria?

a. Zintria lowers the pressure in the eye
b. Zintria increases the chance of chronic dry eye
c. Zintria lowers the concentration of red blood cells in the eye
d. Zintria increases sensitivity to light

Q8a. (Recall of benefits) Answer these questions as best you can based on the information in the ad for Zintria.

[PROGRAMMER: *randomize*]

	True	False
a. It can be taken with aspirin or other pain relievers.		
b. Zintria helps lower your blood pressure.		
c. You take it only once a month.		
d. It can be taken with or without food.		
e. Zintria can reduce your risk of having a stroke.		
f. Zintria is the only high blood pressure medication approved to treat children.		
g. Zintria is proven to help prevent heart attacks.		

Q8b. (Comprehension of benefits)
Please choose a response based on the information you learned in the ad.

[PROGRAMMER: *randomize items and item responses*]

i. What advantage does Zintria have over other treatments for this condition?

a. Zintria is taken only once a month.
b. Zintria is approved to treat more than one type of high blood pressure
c. Zintria helps lower cholesterol
d. Zintria helps you lose weight

ii. Why would your doctor prescribe Zintria for you?

a. To increase my blood circulation.

b. To reduce the risk of liver damage.
c. To reduce the risk of stroke.
d. To decrease my joint pain.

Q9. (Confusion between statement and adequate provision) In the Zintria ad, there were some words written on the screen. Please tell us as much as you can remember about this information. (open-ended)

Codes:

0	No mention of any contact information
1	Mention of adequate provision information only
2	Mentioned some content of toll-free statement but confused it with adequate provision information
3	Some content of toll-free statement/ not confused with adequate provision (adequate provision information can be mentioned also but it is clear that they are distinct)
4	Full content of statement/ not confused with adequate provision

Q10. Which, if any, of the following statements appeared in the ad? You may select more than one.

[PROGRAMMER: *randomize*
Include ONLY the toll-free statement that each participant saw, either a. OR b., NOT both]

a. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.
b. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088 or www.fda.gov/medwatch
c. 800-555-ZINT
d. Clinical trials involved men and women over the age of 18 and were conducted up to 12 months.
e. www.zintria.com
f. Individual results may vary.

[PROGRAMMER: *show the correct statement while Questions 11-14 appear*]

Q11. What does this statement mean to you? (open-ended)

Codes to be determined during pilot testing

Q12. How understandable is this statement?

Extremely understandable
Quite understandable

Moderately understandable
Somewhat understandable
Not at all understandable

[PROGRAMMER: *Include Q12a. only in pilot testing*]

Q12a. Why did you select that answer in the previous question?

(open-ended)

Q13. How confusing is this statement?

Extremely confusing
Quite confusing
Moderately confusing
Somewhat confusing
Not at all confusing

Q14. How clear is this statement?

Extremely clear
Quite clear
Moderately clear
Somewhat clear
Not at all clear

Q15. Have you ever had a serious side effect from a prescription drug?

Yes
No
I'm not sure

Q16. If you had a serious side effect from a prescription drug you were taking, how likely would you be to do each of the following things? {randomize options; j always last}

	Very Likely	Somewhat Likely	Neither Likely nor Unlikely	Somewhat Unlikely	Very Unlikely
a. Call your doctor					
b. Call FDA					
c. Treat with another drug					
d. Go to the					

emergency room					
e. Call the poison control center					
f. Talk to a family member					
g. Talk to a friend					
h. Talk to a pharmacist					
i. Call the drug company					
j. Do nothing					

Q17. If you had a serious side effect from a drug you were taking, which of the following would you do **first**?

[PROGRAMMER: *randomize options; j always last*]

a. Call your doctor
b. Call FDA
c. Treat with another drug
d. Go to the emergency room
e. Call the poison control center
f. Talk to a family member
g. Talk to a friend
h. Talk to a pharmacist
i. Call the drug company
j. Do nothing

Q18. Are you currently taking any prescription drugs for high blood pressure?

Yes
No
I'm not sure

Q19. Have you ever seen any advertising for Zintria before today?

Yes
No
I'm not sure

The following questions may already have been obtained through KN—as long as we have this information in variable form in SPSS, we don't have to ask them again

Q20. Please insert your date of birth.

Q21. Please check your highest level of education.

Some high school
High school graduate
Some college
College graduate
Some graduate experience
Advanced degree (e.g., M.S., M.D., J.D., Ph.D.)

Q22. Are you:

- Hispanic or Latino
- Not Hispanic or Latino

Q23. Which of these best represents your ethnic group? You may choose one or more. Would you say that you are:

- American Indian or Alaska Native
- Asian
- Black or African-American
- Native Hawaiian or Other Pacific Islander
- White

Q24. Gender

- Male
- Female

You have been very helpful. Thank you very much for your participation!