DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

August 25, 2004

Ms. Nancy L. Buc
Ms. Kate C. Beardsley
Buc & Beardsley
919 Eighteenth Street, N.W.
Washington, D.C. 20006-5503

Dear Ms. Buc and Ms. Beardsley:

This letter responds to your May 18, 2004, complaint and request for correction pursuant to Section 515(a) of the Treasury and General Government Appropriations Act for Fiscal Year 2001, Pub. L. No. 106-554, 114 Stat. 2763A-153 (2000), hereinafter referred to as the "Federal Data Quality Act," concerning the Food and Drug Administration's (FDA's) Consumer Campaign on Safe Use of OTC Pain Products. Your complaint was submitted on behalf of your client, McNeil Consumer & Specialty Products (McNeil). Dr. Lester M. Crawford, Acting Commissioner of Food and Drugs, has referred this matter to me for a response.

Your complaint alleges that FDA's campaign, begun on January 22, 2004, and available on FDA's Website at http://www.fda.gov/bbs/topics/NEWS/2004/NEW01008.html, "misrepresent[s] the relative safety of various OTC pain products, representing that acetaminophen products are less safe than nonsteroidal anti-inflammatory drugs (NSAIDs)." Your complaint addresses five specific documents: (1) a reprint of an article from *FDA Consumer* magazine January-February 2003, titled, "Use Caution With Pain Relievers" (FDA *Consumer* Article); (2) two advertisements titled "Why is it important to know that all these medicines contain acetaminophen?" and "The best way to take your over-the-counter pain reliever? Seriously" (Print Ads); (3) a memo to State Boards of Pharmacy titled, "Acetaminophen Hepatotoxicity and Nonsteroidal Anti-Inflammatory Drug (NSAID)-related Gastrointestinal and Renal Toxicity" (Memo); (4) *Questions and Answers on Using Over-the-Counter (OTC) Human Drug Products Containing Analgesic/Antipyretic Active Ingredients Safely* (Q&As); (5) and a Brochure titled, "The best way to take your over-the-counter pain reliever? Seriously." You ask that FDA take the following corrective actions:

1. Halt distribution of the current campaign.

2. Correct the relevant documents before restarting the campaign.

3. Provide an opportunity for McNeil and other companies whose products are affected to comment prior to restarting the campaign and prior to release of any future OTC pain relief drug campaigns or similar ventures.

For the reasons described below, FDA does not agree that this campaign violates the Federal Data Quality Act, *OMB's Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by Federal Agencies* (guidelines), 67 FR 8452 (Feb. 22, 2002) or FDA's own implementing guidance, which is part of the Department of Health and Human Services *Guidelines for Ensuring the Quality of Information Disseminated to the Public*, September 30, 2002.

I. The Campaign as a Whole

On September 19-20, 2002, the Nonprescription Drugs Advisory Committee met to discuss U.S. case report data regarding accidental and unintentional overdoses with acetaminophen- and NSAID-related cases of gastrointestinal (GI) and renal toxicity. One of the suggestions from this meeting was for FDA to conduct a public education campaign to educate consumers about the safe and effective use of pain relievers. After careful consideration of resources, audiences, messages, and dissemination channels, FDA decided that the campaign would initially include two print public service advertisements (one addressing the issue of taking too much acetaminophen and the other focusing on the NSAIDS) and a brochure. In addition, FDA decided to work in partnership with stakeholders on an ongoing effort to continue to get the message out to consumers through a variety of communication channels.

The educational campaign was developed in accordance with our normal policies and procedures for the development of such campaigns. The documents were (1) developed by a team of experts familiar with the drugs and communication specialists, (2) focus tested with the public, (3) circulated and cleared by center managers, and (4) cleared through channels up to and including the Office of the Secretary of Health and Human Services. These policies and procedures provide appropriate safeguards to ensure that the information the agency disseminates meets the Federal Data Quality Act standards.

The Federal Data Quality Act requires agencies to have processes to ensure and maximize the quality, objectivity, utility, and integrity of information disseminated by agencies. The Federal Data Quality Act standards were not meant to be used to impose unnecessary administrative burdens, to inhibit agencies from disseminating important information to the public, nor to second-guess what information agencies determine is appropriate for dissemination to the public. After re-examining the educational campaign in light of your complaint, it is FDA's position that its decisions regarding which products and risks to discuss in light of the current public knowledge about these products and the recent discussions by the advisory committee were more than reasonable and fall well within the standards set out by the Federal Data Quality Act and relevant guidelines.

You allege that the campaign violates the Federal Data Quality Act standards for objectivity because the documents that are the subject of the complaint "present the risks from acetaminophen in detail, while vastly understating the risks of NSAIDs, especially aspirin." You also allege that the campaign is untruthful, in that it implies that acetaminophen is more dangerous than NSAIDs, when, in your opinion, it is not.

We disagree that the campaign violates the Federal Data Quality Act standards for objectivity. McNeil concedes that the FDA News Release, the Science Background, and the Health Hints documents, which are part of the campaign, provide a reasonably balanced statement of the risks of the various products (Letter at 4). The fact that in some parts of the campaign FDA has chosen to focus on the risks from acetaminophen specifically and not in detail on the risks of NSAIDs or aspirin does not render the campaign as lacking in objectivity in violation of the Federal Data Quality Act standards. FDA may choose what risks to focus on in a specific public education campaign. As long as those risks are accurately characterized, the fact that other risks are not discussed, or are discussed in some parts of the campaign but not others, does not render the campaign in violation of the Federal Data Quality Act standards.

Furthermore, the campaign cannot be viewed in isolation. On other occasions, the agency has provided information to consumers on aspirin or NSAIDs, without commenting on acetaminophen.[1] The Federal Data Quality Act standards do not prevent Federal agencies from making choices as to what risks to emphasize in specific public education campaigns and what to emphasize in other ways. They cannot be interpreted to require an agency to discuss all competing products and to give equal time to all potential risks in each communication. If that were the case, the important public health information an agency was trying to convey would be lost among all the other competing information.

In the discussion of whether the FDA campaign is untruthful, you suggest that NSAIDs are more dangerous than acetaminophen, citing GI bleeds and the National Consumers League statement that GI bleeding caused by NSAID use accounts for as many as 16,000 deaths a year (Letter at 7). However, the campaign at issue is directed at OTC use. Much of the morbidity and mortality associated with the use of NSAIDs is in the prescription or professional label setting, where NSAIDs are taken in higher doses and/or for longer periods of time because they are used to treat serious diseases and prevent cardiovascular events. FDA does not agree that OTC NSAIDs are more dangerous than OTC acetaminophen. Therefore, we disagree with your assertion that the campaign is untruthful.

You have provided specific comments directed at selected pieces of the education campaign. We address each of your concerns in the remainder of this response.

II. Public Service Advertisements (PSAs or ads)

You assert that the print ads lead a consumer to "surely believe that FDA views acetaminophen as far more dangerous than NSAIDs" (Letter at 5). You provide the following comments to support your contention.

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[1] http://www.fda.gov/bbs/topics/CONSUMER/CON00296a.html ; http://www.fda.gov/bbs/topics/CONSUMER/CON00034.html ; Aspirin Education:
print PSA - http://www.fda.gov/cder/consumerinfo/dailyasp_psa_low.pdf
brochure - http://www.fda.gov/cder/consumerinfo/dailyasp_brochure_low.pdf
fact sheet - http://www.fda.gov/cder/consumerinfo/AspirinFactSheet.pdf
FDA Consumer Magazine - http://www.fda.gov/fdac/features/2003/503_aspirin.html

- One ad is directed exclusively at acetaminophen while the other is directed at OTC pain relievers in general.
- The acetaminophen PSA discusses the risks of acetaminophen use in the subheading while the second PSA (to which you refer as the NSAID PSA) frames the subheading as suggestions to consumers.
- The acetaminophen ad uses larger type and contains two bolded statements about liver damage while the NSAID ad buries the risks in small print.
- The NSAID ad does not refer to the risks related to overdose at all.
- The central message of the acetaminophen ad is that acetaminophen can cause liver damage while the central message of the NSAID ad is that consumers should know the active ingredients in their pain relievers.
- There is no reason to have two ads. It would be more useful to collapse the message into one ad that communicates the whole message in one place.

We disagree with your assessment that the print ads will lead someone to believe that FDA views acetaminophen as far more dangerous than NSAIDs. The headings in the NSAID ad present a hypothetical question to consumers on how they should take pain relievers. The answer "Seriously" will encourage them to find out why. As the consumer reads further in the text, it is clear that the ad references only NSAIDs. NSAID ingredients are underlined (to highlight them) in the first line after the subheadings. Acetaminophen is not mentioned at all in the ad. The ad clearly states that NSAIDs may cause stomach bleeding or kidney problems in some people. This is the reason consumers should take them seriously. There are no comparative statements about the relative safety of acetaminophen to NSAIDs that would suggest we find NSAIDs to be safer than acetaminophen. We have made no relative comparison in either ad to suggest one is safer than the other. The issue of OTC NSAID overdose is not a major area of concern, and we did not believe it necessary to include it in the NSAID ad. There is additional discussion of this issue in our response to your comments on the *FDA Consumer* article.

We believe that the ads appropriately emphasize the relative risks of these products. Although format and style can be important, we note that your criticisms of these ads generally do not address the content of the ads. We do not believe that Congress intended for the Federal Data Quality Act standards to require Federal agencies to engage in discussions that do not materially affect the quality of the information it is disseminating. In the NSAID ad, however, it is a reasonable suggestion that we make format changes to highlight stomach bleeding and kidney problems if we use the ad in the future.

III. The *FDA Consumer* Article

You state that the *FDA Consumer* article is even less balanced than the PSAs for the following reasons:

- Eight clear and focused paragraphs are devoted to acetaminophen, but only three short paragraphs without detail are devoted to NSAIDs.
- The sections on acetaminophen devote special attention to overdose in children, but the paragraphs on NSAIDs do not mention overdose or any pediatric issues.
- Reye's syndrome associated with aspirin is not discussed.

- The acetaminophen section discusses the alcohol warning, but the NSAID discussion does not.
- Overdose is not mentioned in the discussion of NSAIDs, while the acetaminophen paragraphs are devoted entirely to overdose.

Your primary complaint about the article involves the amount of discussion regarding acetaminophen relative to NSAIDs. You point out that other adverse events related to NSAIDs are not included in the article, but argue they should be included. We disagree.

The *FDA Consumer* article included in the educational campaign was initially published in the January 2003 *FDA Consumer* magazine. It was intended to inform consumers about the discussions at the advisory committee meeting. It was not intended to provide a complete overview of the safety of any of the products. Except for some slight revisions to update it for the educational campaign, the content of the article was essentially unchanged. The message conveyed in the article used in the campaign was similar to the message in the original article.

The article provided a balanced discussion of the risks and benefits of acetaminophen. The introductory sentence of the article stated, "Acetaminophen is a safe and effective pain reliever that benefits millions of consumers. However, taking too much could lead to serious liver injury." The amount of information included in the article on each topic was the amount necessary to clearly explain the different situations with regard to the unintentional overdose of acetaminophen and GI bleeding associated with NSAIDs. The number of paragraphs devoted to acetaminophen versus NSAIDs represents the amount of space needed to describe the situation for each type of ingredient. The failure of people to use acetaminophen correctly, leading to significant liver toxicity, suggests that consumers do not understand the consequences of ingesting too much acetaminophen. If the article had not adequately described the situation with regard to acetaminophen, it actually could have led the reader to believe that acetaminophen was less safe than NSAIDs, rather than safe when used in accordance with the label and with knowledge of the active ingredients in other medications.

With regard to overdose, a discussion of overdose was not included for NSAIDs, but it was for acetaminophen for the following reasons: The hepatotoxicity associated with acetaminophen is of particular concern in the context of unintentional overdose, but the GI bleeding associated with NSAIDs is of concern at the recommended doses of NSAIDs. Therefore, for NSAIDs, the article made the point that there is a risk even at recommended doses. There was no need to include a discussion of overdose of NSAIDs.

Additionally, it would be inappropriate to suggest that the consequence of overdose with NSAIDs is on a par with overdose of acetaminophen. Doubling the maximum daily OTC dose of acetaminophen for several days presents a significant risk for developing liver toxicity. Doubling the maximum daily recommended OTC dose of an NSAID for several days would be the prescription dose. Although this may slightly increase a person's risk for bleeding, it is not even close to the seriousness presented by doubling the dose of acetaminophen.

The discussion on alcohol in the article reflects the discussion at the advisory committee meeting. For acetaminophen and alcohol, the data presented at the advisory committee meeting

and the ensuing discussion supported the current alcohol warning on acetaminophen products. For NSAIDs and alcohol, the data presented at the advisory committee meeting and the ensuing discussion questioned the accuracy of the current alcohol warning on NSAID products. Numerous members of the committee stated that the alcohol warning on NSAIDs should be removed. At the time the *FDA Consumer* article was written, FDA had not decided whether the alcohol warning should be removed from NSAIDs. Because a decision had not been made on whether to change the NSAID alcohol warning, the agency made a reasonable decision not to discuss the issue.

We disagree with your suggestion that the NSAIDs discussion should have addressed Reye's syndrome. Reye's syndrome associated with aspirin use is essentially nonexistent now in the United States. In the 1980s, FDA initiated an educational campaign on the relationship between aspirin and Reye's syndrome because hundreds of cases were reported each year. The *FDA Consumer* magazine published a separate article on Reye's syndrome in November 1990. Because of FDA's Reye's syndrome campaign and the education of consumers by other agencies and groups, the number of cases of Reye's syndrome decreased dramatically over several years before any labeling changes were initiated.

Finally, as stated previously, this educational campaign should not be viewed in isolation. FDA addresses different risks in different forums. For example, the *FDA Consumer* magazine addressed the NSAID aspirin's risks in a September 2003 article entitled "Daily Aspirin Therapy." The article pointed out that "FDA's Center for Drug Evaluation and Research (CDER) has launched a public education campaign to remind consumers that aspirin is not without risk." The article was directed at consumers who would use aspirin for cardio-prevention without a doctor's advice. It outlined the importance of seeking physician advice because of risks related to chronic aspirin use. There is a discussion of risk associated with aspirin use. There is no mention of acetaminophen hepatotoxicity.

IV. The State Boards of Pharmacy Memo

You assert that the Memo contains less obvious, but still important, examples of bias. You provide the following examples:

- The Memo says "the purpose of the advisory committee [meeting] on which the memo reports was to review the data on unintentional acetaminophen overdose and determine whether additional measures should be taken to decrease the risk of these events" (Letter at 6) and does not state that NSAID risk was also discussed at the meeting.

- The Memo states that acetaminophen overdose can lead to liver failure, which may lead to liver transplant or death, but there was no comparable mention of death associated with NSAID-related GI bleeding.

- The language in the Memo directed at container labeling mentions acetaminophen, but not NSAIDs.

- NSAID overdose due to taking multiple preparations containing NSAIDs was also discussed by the advisory committee, but was not included in the Memo.

With regard to the first example, you note that the Memo says "the purpose of the advisory committee on which the memo reports was to review the data on unintentional acetaminophen overdose and determine whether additional measures should be taken to decrease the risk of these events" (Letter at 6). You assert that there is not even a suggestion that NSAID risk was also a purpose of the meeting. Your characterization of the content of the Memo is inaccurate. The language you quote was located in a section describing acetaminophen toxicity. The introductory paragraph of the Memo makes clear that NSAID toxicity was also a part of the discussion at the advisory committee meeting. The second sentence of the first paragraph of the Memo states, "On September 19-20, 2002, the Nonprescription Drugs Advisory Committee, with experts from other committees, discussed available U.S. case report data regarding accidental and unintentional overdoses with acetaminophen and NSAID-related cases of gastrointestinal (GI) and renal toxicity."

You point out that the Memo states that acetaminophen overdose can lead to liver failure, which may lead to liver transplant or death. You note there was no comparable mention of death associated with NSAID-related GI bleeding. We do not believe this criticism has merit. The Memo was directed to pharmacists and other health professionals who regulate the practice of pharmacy for each state. As the Memo notes, most health professionals are aware of the GI bleeding and renal toxicity associated with NSAIDs, particularly prescription NSAIDs, and the fact that these adverse events can lead to death. We believe they are not aware of the problem associated with the unintentional overdose of acetaminophen leading to liver toxicity. It was important to alert them to the seriousness of this toxicity. The Memo alerted them to the unappreciated problem of unintentional overdose with acetaminophen and reminded them of the previously recognized adverse GI bleeding and renal toxicity associated with NSAIDs. We believe the Memo provides the appropriate context for each type of pain reliever.

Finally, you note the language in the Memo directed at container labeling mentions acetaminophen, but not NSAIDs. You point out that NSAID overdose due to taking multiple preparations containing NSAIDs was also discussed by the advisory committee, but was not included in the Memo. Once again, you have focused on one specific paragraph of the Memo while ignoring other portions relevant to this issue. There was very little discussion of NSAID overdose at the advisory committee meeting and few, if any, data presented at the meeting suggesting a significant increase in risk by taking more than the recommended amount of an OTC NSAID over several days. That is not the case for acetaminophen. There are clearly cases of acetaminophen overdose where doubling the dose for several days has led to serious liver toxicity. Given the scenario of doubling the daily maximum OTC dose of acetaminophen for 5 days versus doubling the maximum OTC dose of an NSAID for 5 days, we would be more concerned about the risk of liver toxicity related to acetaminophen. Based on the data from the individual cases discussed at the advisory committee meeting, it is evident that liver toxicity related to repeated excess doses of acetaminophen over several days is not responsive to conventional treatment with acetylcysteine (the antidote for acetaminophen poisoning). Consequently, it was important to caution pharmacists that (1) there are more than 200 approved prescription products containing acetaminophen, (2) container labeling often abbreviates the

name of the drug making it difficult for some patients to identify, and (3) some of the toxicity has been attributable to patients ingesting prescription and OTC acetaminophen containing products concurrently. As a last point, contrary to your assertion that labeling recommendations are directed entirely at acetaminophen, other portions of the Memo do provide recommendations for labeling prescription NSAID products.

V. The Questions and Answers and Brochure

Your last criticism of the campaign focuses on the Q&As and the Brochure. You provide the following examples of what you consider bias:

- Acetaminophen overdose is described as "severe," but a similar characterization was not provided for GI bleeds and kidney injury related to the use of NSAIDs.
- The Q&As describe the occurrence of stomach bleeding from aspirin and other NSAIDs as rare. You state that no such calming language was used with respect to acetaminophen overdose.
- The brochure used the word "serious" to describe acetaminophen related liver damage, but not NSAID-related adverse events.

Your comments take statements in the Q&As out of context. The Q&A to which you refer in the first example (question 2) describes the discussion at the advisory committee meeting and does not discuss the type of injury associated with each ingredient. The answer to question 2 states, "Specifically, the committee reviewed cases of *severe* liver injury [emphasis added] associated with the use of acetaminophen. They also reviewed cases of stomach bleeding and kidney injury related to the use of aspirin and NSAIDs." This answer is factually correct. The committee did not review less serious cases of acetaminophen hepatotoxicity.

You also note that the Q&As describe the occurrence of stomach bleeding from aspirin and other NSAIDs as rare. You state that no such calming language was used with respect to acetaminophen overdose. You are referring to the answer to question 3 ("How do consumers take these medications safely?"), and you have taken the term "rare" out of context. The answer to question 3 does not even mention liver injury associated with acetaminophen. In fact, there is no mention of liver injury in any of the other questions outside of the reference to the discussion at the advisory committee meeting in the answer to question 2, which we have already said was factually correct.

The discussion for NSAIDs, however, mentions stomach bleeding and provides risk factors. It puts the risk into context in the following manner: "Although it is rare for these events to occur when using OTC doses and for short periods of time, some people do develop bleeding." It would be difficult to incorporate the word "rare" related to acetaminophen liver injury because liver injury is not even discussed in the Q&As. If anything, an appropriate remedy would be to include more information on the risk of acetaminophen-related injury. Additionally, any suggestion that the events are rare with an overdose of acetaminophen is not the message the educational campaign hopes to convey. This would lead consumers to believe that it is all right

to take more because serious adverse events would be rare. This is not true and would undermine the purpose of the campaign.

You also note that the Brochure used the word "serious" to describe acetaminophen-related liver damage, but not NSAID related adverse events. You fail to mention that "serious" was also used in the first paragraph of the Brochure. It was used in the context of describing problems when used by people with certain conditions or taking certain medications. Later in the Brochure, it is evident that "serious" is referring to NSAIDs. When describing problems in people who use too much, the first paragraph simply uses the word "problems" and not "serious problems." Later in the Brochure, it is evident that this reference to too much was related to acetaminophen. You also fail to note that the three Drug Fact labels depicted in the Brochure listed an NSAID as the active ingredient. If anything, failure to include acetaminophen as one of the active ingredients in one of the Drug Facts labels could be construed as unfairly emphasizing NSAIDs.

VI. Conclusions

In summary, we do not believe the educational campaign taken as a whole, or in any of its parts, violates the Federal Data Quality Act standards for objectivity, nor do we believe the campaign understates the risks of NSAIDs or implies that acetaminophen is more dangerous than NSAIDs. Accordingly, we decline to take the corrective action you request.

In accord with FDA's implementing guidelines, if you do not agree with this decision on your complaint, you may send a request for reconsideration within 30 days of receipt of this decision. Your request for reconsideration should be designated as an "Information Quality Appeal" and should include a copy of your original request as well as this decision. Your appeal should state the reasons why you believe this response to your complaint is inadequate.

Sincerely,

Steven Galson, M.D., M.P.H
Acting Director
Center for Drug Evaluation and Research

CC: FDA's Office of the Ombudsman