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May 18, 2004

Lester M. Crawford, D.V.M., Ph.D.
Acting Commissioner of Food and Drugs (HF-1)
Food and Drug Administration
5600 Fishers Lane
Room 14-71
Rockville, MD 20857

Re: Complaint and Request for Correction Pursuant To Federal Data Quality Act Concerning "Consumer Campaign on Safe Use of OTC Pain Products"

Dear Dr. Crawford:

On behalf of McNeil Consumer & Specialty Products ("McNeil"), which we represent, Buc & Beardsley, located at the address and phone numbers listed above, submits this complaint and request for correction (the "Complaint") under the Federal Data Quality Act (the "FDQA").[1] McNeil markets Tylenol® (acetaminophen) single ingredient and combination-ingredient products, Motrin® (ibuprofen) products, and St. Joseph® low strength aspirin. The Complaint concerns FDA's "Consumer Campaign on Safe Use of OTC Pain Products" (the "Campaign"). The Campaign began on January 22, 2004 and the associated documents remain available on FDA's website at http://www.fda.gov/bbs/topics/NEWS/2004/NEW01008.html. McNeil understands that FDA intends to republish the materials through various distribution outlets, including print publications. The primary documents at issue are:

(1) A reprint of an article from FDA Consumer magazine, January-February 2003, titled "Use Caution With Pain Relievers" ("FDA Consumer Article"), annexed as Exhibit A;

(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"), annexed as Exhibit B.

Other documents that are part of the Complaint are a memo to State Boards of Pharmacy titled "Acetaminophen Hepatotoxicity and Nonsteroidal Anti-Inflammatory Drug (NSAID)-related Gastrointestinal and Renal Toxicity" ("Memo to State Boards"), annexed as Exhibit C; "Questions and Answers on Using Over-the-Counter (OTC) Human Drug Products Containing

1. Section 515(a) of the Treasury and General Government Act for Fiscal Year 2001, Pub. L. No. 106-554 (Appendix C), 114 Stat. 2763A-153 (2000).

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Analgesic/Antipyretic Active Ingredients Safely" ("Q and A"), annexed as Exhibit D; and a brochure titled "The best way to take your over-the-counter pain reliever? Seriously" ("Brochure"), annexed as Exhibit E.

The documents at issue and, as a result, the Campaign as a whole misrepresent the relative safety of various OTC pain products, representing that acetaminophen products are less safe than nonsteroidal anti-inflammatory drugs (NSAIDs).[2] The false representation can be expected to influence consumers to make pain relief choices that are not in the best interest of promoting health and safety. In addition to misleading consumers, the Campaign is expected to negatively affect McNeil, the world's largest marketer of OTC acetaminophen products.

To mitigate the adverse effects of FDA's actions, McNeil requests that FDA take the following corrective actions:

(1) Halt distribution of the current Campaign;

(2) Correct the relevant documents before restarting the Campaign; and

(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.

The Legal Standard and Its Applicability to the Campaign

The purpose of the FDQA is to ensure the quality of information that federal agencies disseminate and establish mechanisms to correct information that does not meet these quality standards. The FDQA directed the Office of Management and Budget ("OMB") to issue guidelines, which each agency must use to prepare its own guidelines addressing methods to accomplish these information quality objectives. OMB's guidelines require that each agency adopt a standard of quality and incorporate information quality criteria, including quality review before information is disseminated, into agency dissemination practices.[3] OMB defines quality to include utility, objectivity and integrity.[4]

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2. As FDA has acknowledged in the past, both acetaminophen and NSAIDs are safe for OTC use. See, e.g., Internal Analgesic, Antipyretic and Antirheumatic Products for Over-the-Counter Human Use; Tentative Final Monograph, 53 Fed. Reg. 46,204 (Nov. 16, 1988) (proposing the establishment of conditions under which acetaminophen and aspirin are GRAS/E analgesic/antipyretic ingredients); Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use; Proposed Amendment of the Tentative Final Monograph, and Related Labeling, 67 Fed. Reg. 54,139 (Aug. 21, 2002) (proposing the establishment of conditions under which ibuprofen is a GRAS/E analgesic/antipyretic ingredient) ("Ibuprofen Proposed Amendment").

3. Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by Other Agencies ("OMB guidelines"), 67 Fed Reg. 8452, 8458-59 (Feb. 22, 2002).

4. Id. at 8459.

The concept of objectivity, which is most relevant here, is divided into presentation and substance:

- Presentation is explained as "[w]hether information is being presented in an accurate, clear, complete and unbiased manner. This involves whether the information is presented within a proper context. Sometimes, . . . other information must also be disseminated in order to ensure an accurate, clear, complete, and unbiased presentation."[5]

- Substance is defined to mean "a focus on ensuring accurate, reliable, and unbiased information."[6]

The requirement for objectivity encompasses several ideas that are familiar from FDA and FTC evaluations of private sector promotional practices. A document or set of documents may be literally true, that is, each statement taken alone may be accurate, but still misleading because, for example, it omits material facts or unduly emphasizes one fact over another or creates misleading comparisons.[7]

OMB also makes the point that information likely to be influential in affecting individual behavior deserves particular scrutiny. Among the principles articulated by OMB is that "[t]he more important the information, the higher the quality standards to which it should be held, for example, in those situations involving 'influential scientific . . . information.'"[8]

Pursuant to the OMB guidelines, HHS adopted guidelines, of which FDA's guidelines are a part, applying to information disseminated by HHS agencies, including "[a]uthoritative health, medical and human services information aimed at consumers and health and human services professionals."[9] The FDA guidelines are more specific than the HHS guidelines, stating that the guidelines cover "consumer advice and fact sheets," "public health and safety alerts" and "various subject matter brochures intended for consumers."[10] FDA defines influential

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5. Id.

6. Id.

7. Federal Food, Drug, and Cosmetic Act § 201(n); Federal Trade Commission Act § 15(a). See generally 21 C.F.R. § 202.1(e)(6)-(7); FTC Policy Statement on Deception (Oct. 14, 1983), available at http://www.ftc.gov/bcp/policystmt/ad-decept.htm.

8. OMB guidelines, 67 Fed. Reg. at 8452.

9. U.S. Department of Health and Human Services Guidelines for Ensuring the Quality of Information Disseminated to the Public ("HHS guidelines"), Part I.D.4.b. (Sept. 30, 2002). FDA's guidelines are located in Part II.F. of the HHS guidelines.

10. FDA guidelines (HHS guidelines, Part II.F.) at § III.A. FDA's guidelines also establish methods for making complaints and requests for correction, and describe several offices to which complaints may be directed, including to the agency official who is the supervisor of the employee who made the decision or to the FDA ombudsman. FDA has committed to respond within 60 days. Id. at § VI.B.-C. Because the documents at issue were released by FDA and probably were drafted by CDER, McNeil believes that you are the relevant supervisor.

information in part as disseminated information that results from agency actions that will adversely affect in a material way "competition" or "public health or safety."[11]

The documents at issue in this Complaint have been and are being disseminated by FDA. They purport to be authoritative health and medical information providing consumer advice. They can be expected to be understood by the millions of consumers who take OTC pain products as accurate and not misleading scientific information and to have an important influence on the choices consumers make, which will affect both public health and safety and competition. The FDQA therefore not only applies to these documents, but also requires a high level of objectivity, both in the substance of information presented and in the manner in which it is presented. The documents at issue are not objective, and, therefore, must be corrected.

The FDA Consumer Article and the Print Ads Are Not Objective.

The purpose of the Campaign, titled "Safe Use of OTC Pain Products," is to "provide advice on the safe use of" OTC acetaminophen and NSAID products so that consumers can make wise choices in using any or all of the products. The FDA News Release (annexed as Exhibit F), Science Background (annexed as Exhibit G), and Health Hints (annexed as Exhibit H) documents that are part of the Campaign reflect that purpose, providing a reasonably balanced statement of the risks of the various products. While there are some features of these documents that emphasize the risks of acetaminophen over those of NSAIDs, and although McNeil would prefer that these documents distinguish more sharply between risks inherent in using labeled doses and risks related to overdose, McNeil believes that these documents represent a good faith and largely successful effort to provide a balanced picture of the risks. In these documents, the allocation of space to each product class, the tone of the discussion of each class, and the information provided to consumers are appropriately matched.

The Campaign as a whole and especially the documents that are the subject of this Complaint, however, do not present an accurate, clear, complete and unbiased statement of the risks associated with acetaminophen and NSAIDs. They present acetaminophen risk in detail, while vastly understating the risks of NSAIDs, especially aspirin.

McNeil has no objection to communicating acetaminophen risks, and this Complaint is neither intended to keep FDA from publicizing acetaminophen risks nor to seek any acetaminophen-related correction to the Campaign documents. As you may know, McNeil itself has taken steps to communicate the same messages, having recently received permission from FDA to incorporate in its labeling a warning regarding liver damage associated with untreated acetaminophen overdose; spearheading a public relations campaign, in cooperation with the National Council on Patient Information and Education, on overdose; and submitting a petition to clarify information on pediatric use of acetaminophen.[12] McNeil does object, however, to presenting those risks in a context that vastly understates NSAID risk and, therefore, amounts to an invalid comparison of acetaminophen and NSAID risk.

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11. Id. at § VII.A.

12. Citizen Petition from McNeil Consumer Healthcare, Docket No. 77N-0094/CP14 (Feb. 1, 1999).

(1) The Representation Created by the Campaign

One need look no farther than the headlines of the two print ads to identify the message that they communicate. One ad, "Why is it important to know that all these medicines contain acetaminophen," is directed exclusively at acetaminophen. The other ad, "The best way to take your over-the-counter pain reliever? Seriously," is directed at OTC pain relievers in general. Thus, a consumer scanning these ads would be focused on acetaminophen, but not on NSAIDs.

Both ads also contains subheads. The subhead for the acetaminophen ad reads "Because too much can damage your liver." The subhead for the NSAID ad reads "Know the active ingredients in your pain relievers. Read the labels." Thus, the acetaminophen subhead focuses on the specific risk at issue. The NSAID subhead says nothing about risk, but rather is framed as suggestions to the consumer.

Both ads then proceed to a paragraph of text. The acetaminophen ad, in which larger type is used, contains another bolded statement about liver damage. The NSAID ad buries the risks in small print without emphasis. Further, although the acetaminophen ad is directed entirely toward risk associated with overdose, the NSAID ad does not refer to risks related to overdose at all.

The result is that, in contrast to the central message of the acetaminophen ad, that acetaminophen can cause liver damage, the central message of the OTC pain reliever ad is that consumers should be sure to know the active ingredients in their pain relievers. Any consumer seeing the ads would surely believe that FDA views acetaminophen as far more dangerous than NSAIDs.

Further, there is no reason to have two ads. The media who are being encouraged to run these ads are not likely to pick up both ads, and are, we believe, more likely to pick up the acetaminophen ad because the message appears stronger. It would be more useful to collapse the message into one ad that would communicate the whole message in one place.

The FDA Consumer article is even less balanced. Eight paragraphs, including the introductory paragraph, are devoted to a detailed, clear and focused description of acetaminophen. Three short paragraphs without detail make a mild statement about NSAID risk. The sections on acetaminophen devote special attention to overdose problems in pediatric dosing. The paragraphs on NSAIDs do not mention either overdose issues or Reyes Syndrome; in fact they fail to mention pediatric issues at all. The acetaminophen discussion discusses the alcohol warning on acetaminophen; the NSAID discussion does not mention the same alcohol warning on NSAIDs. The NSAID paragraphs deal with risks inherent in the labeled use of the product and do not mention overdose as an issue; the acetaminophen paragraphs are devoted entirely to overdose. As a result of these and other omissions and the overt bias in the article, the net impression of the article, which purports to be about pain relievers in general, is that acetaminophen is far more dangerous than NSAIDs.

In addition, three other documents contain less obvious but still important examples of bias. The Memo to State Boards prominently states that acetaminophen overdose may cause liver failure, which may lead to liver transplant or death. The section on NSAIDs says merely that adverse events such as GI bleeding and renal toxicity are well known. No comparable message that these too may result in death is communicated. In fact, there is no discussion of adverse events due to overdose for NSAIDs. The Memo to State Boards says that 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."[13] Although one full day during the two day meeting was devoted to NSAIDs, there is not even a suggestion that NSAID risk was also a purpose of the meeting or that "additional measures" might be taken as to them. The request for assistance in addressing container labeling requirements for prescription products is directed entirely at acetaminophen, although NSAID overdose due to taking multiple preparations containing NSAIDs was also discussed by the advisory committee and is discussed earlier in the memo to state boards.

The Q and A and Brochure raise similar issues. In the Q and A, the liver injury that can result from acetaminophen overdose is described as "severe."[14] The GI bleeds and kidney injury related to the use of aspirin and NSAIDs are not characterized. The Brochure has the same problem. There, the acetaminophen liver injury is characterized as "serious," while NSAID-related adverse events are not.[15] In the Q and A, the risk of stomach bleeding from aspirin and NSAIDs is characterized as "rare"; no such calming language was used with respect to acetaminophen overdose.[16] Again, no discussion on NSAID overdose is included.

Any uncertainty about what these pieces represent can be immediately resolved by reviewing the press coverage that the unveiling of the Campaign engendered. For example, the second sentence of the Associated Press story read as follows: "The biggest concern: Taking too much of the popular drug acetaminophen can poison the liver."[17] The following four paragraphs of the story expanded on that theme. Associated Press stories are routinely picked up by over a thousand newspapers. Yahoo, which receives 113,000,000 visitors a month, carried a link to the AP story on its home page for a day. Broadcast media also picked up the story; the overriding message was that the FDA is most concerned about acetaminophen. For example, one FOX affiliate warned, "The FDA said the biggest problem is taking too much of a popular drug best known under the Tylenol brand."[18] By contrast, McNeil located no media stories that led with NSAIDs. In short, the Campaign represents, and has been thus far understood to mean, that there should be greater concern about acetaminophen than about NSAIDs.

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13. Memo to State Boards at 1.

14. Q and A at 1 (answer to Question 2).

15. Brochure at 2.

16. Q and A at 1 (answer to Question 3).

17. Lauran Neergaard, Misusing Painkillers can be Fatal, FDA Warns, Detroit Free Press (Jan. 27, 2004), available at http://www.freep.com/news/health/pain27_20040127.htm.

18. Today in Florida, WSVN-TV (FOX) Miami/Ft. Lauderdale (Jan. 24, 2004, 8:00 - 8:30 am).

(2) The Representation is not Truthful

The truth is that acetaminophen is not more dangerous than NSAIDs and that there should not be greater concern about acetaminophen than NSAIDs.

Use Within Labeled Directions: Unlike acetaminophen, NSAIDs cause serious adverse events when taken as directed in the labeling. GI bleeds, renal failure, and Reyes Syndrome in children are the most obvious examples.[19] According to the National Consumers League, "Overall, GI bleeding caused by NSAID use is now recognized as the most common, serious adverse drug reaction in the United States, and accounts for as many as 16,000 deaths a year."[20] FDA's notice of final rulemaking regarding professional labeling for aspirin describes adverse experiences that include renal insufficiency, prolonged prothrombin time, acute anaphylaxis, and asthma.[21] Various drug interactions are noted, and general precautions include renal failure, hepatic insufficiency, and patients on a sodium-restricted diet (e.g., patients with congestive heart failure).[22] FDA has recently proposed that all NSAIDs carry an allergy warning that speaks to hives, facial swelling, asthma, and shock, a subject that is entirely absent from the Campaign.[23] NSAIDs carry a warning that they are not for use in the last three months of pregnancy, another fact that seems central to safe use, but which is absent from the Campaign. Acetaminophen carries no such warnings, nor does it need them. Both acetaminophen and

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19. In September 2002, FDA convened a two day Nonprescription Drugs Advisory Committee ("NDAC") meeting to discuss risks related to acetaminophen and NSAIDs and asked NDAC for recommendations on steps that could be taken to reduce risk (the "NDAC meeting"). NDAC made a number of recommendations on labeling of these products, on which FDA has not yet taken regulatory action. At the NDAC meeting, the committee reviewed in detail the data on GI bleeds and renal effects associated with NSAIDs and recommended that a direct warning on GI bleeds and liver cirrhosis be added to NSAID labels. The Committee also recommended that increased risk to certain subpopulations be made explicit in the label, including individuals over 65, those taking corticosteriods or anticoagulants, those having a history of ulcers, and those taking other NSAIDs. NDAC Sept. 20, 2002 meeting Transcript ("Sept. 20th Transcript") at 216-220.

20. Sept. 20th Transcript at 22.

21. Internal Analgesic, Antipyretic and Antirheumatic Drug Products for Over-the-Counter Human Use; Final Rule for Professional Labeling of Aspirin, Buffered Aspirin, and Aspirin in Combination With Antacid Drug Products, 63 Fed. Reg. 56,802, 56,816 (Oct. 23, 1998) ("Aspirin Final Rule").

22. Aspirin Final Rule, 63 Fed. Reg. at 56,816.

23. Ibuprofen Proposed Amendment, 67 Fed. Reg. at 54,151.

NSAIDs carry alcohol warnings, although the FDA Consumer Article mentions alcohol only in connection with acetaminophen.[24]

Overdose: Both acetaminophen and NSAIDs can cause serious adverse effects when consumers overdose,[25] and both acetaminophen and NSAIDs can be found in multiple combination drugs, both OTC and prescription, which increases the risk of overdose for both. Because the NSAIDs category includes so many active ingredients, however, it will be correspondingly more difficult to teach consumers to identify them so that they can avoid concomitant doses.[26]

It is true that the liver damage associated with acetaminophen overdose is a serious complication that can lead to fatalities. It is also true that as a percentage of exposures, NSAIDs cause more fatalities. American Association of Poison Control Center (AAPCC) data from 1987 to 1996 show that aspirin has a higher percentage of fatalities per exposure than does acetaminophen.[27] If acetaminophen use decreased while aspirin and other NSAID use increased, available data suggest that more people would die from aspirin and other NSAID-related gastrointestinal bleeding than those potentially spared from acetaminophen overdose hepatotoxicity.[28]

(3) The Campaign Is Not Objective

FDA cannot seriously argue that NSAIDs are safer than acetaminophen, and McNeil does not believe that FDA intended to create that impression. Whatever its intent, however, the

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24. The Campaign as a whole is more than a little inconsistent on the subject of increased risks associated with regular alcohol use. The FDA Consumer Article, Q&A, and Health Hints discuss alcohol in connection with acetaminophen but not NSAIDs. The Science Background mentions alcohol as an issue for both acetaminophen and NSAIDs, but not in parallel format. NDAC was unsure that alcohol should be mentioned as a risk factor for either. Sept. 20th Transcript at 251-254.

25. Unlike some of the adverse effects of NSAIDs, either when taken as directed or when overdosed, the adverse effects of acetaminophen overdose are safely and easily reversed if identified early enough.

26. This problem is especially acute with NSAIDs because many consumers chronically take low doses of aspirin to prevent cardiovascular events, and then add an NSAID when they are ill. There are no chronic uses of acetaminophen.

27. AAPCC data quoted in FDA's Proposed Ibuprofen Amendment to make ibuprofen part of the OTC Review report 450 fatalities from 312,618 acetaminophen exposures, and 401 fatalities from 153,495 aspirin exposures. Ibuprofen Proposed Amendment, 67 Fed. Reg. at 54,147.

28. McNeil's review of the data and its calculations supporting this statement, as well as a chart showing estimated annual excess mortality associated with analgesic use, are annexed as Exhibit I (Letter and Background Package from Paula J. Oliver, Senior Director, Medical and Regulatory Science, McNeil Consumer and Specialty Pharmaceuticals, to Sandra Titus, Ph.D., Advisors and Consultants Staff (HFD-021), FDA/CDER (Sept. 3, 2002) at 15-16).

agency has done so by vastly understating NSAID risk.[29] The Campaign is not accurate, reliable or complete because it omits important material information, and it is biased because of the way the information that is included is presented.

It is more than a little ironic that FDA, which regularly disciplines drug manufacturers for misleading promotion, omission of material information, and unsubstantiated comparisons, should itself engage in such practices. Consumers expect objectivity from FDA; the agency is perceived, usually rightly, as an independent unbiased protector of the public's interest. When FDA speaks, consumers pay attention. Therefore, it is especially important that FDA's messages be correct.

Consequences of the Campaign

Because the Campaign tells consumers that FDA believes acetaminophen is more dangerous than NSAIDs, one can expect that more consumers will choose NSAIDs, and fewer acetaminophen. This will not promote either the public's safety or the public's interest. For all the reasons described above, many responsible consumers, which McNeil believes most consumers to be,[30] are far safer taking acetaminophen than aspirin. Further, it is not in the public's interest for the government to influence for no reason the allocation of the market share among competing companies.

This is not to say that FDA should have no role in helping consumers make wise choices about what pain drugs to take. FDA can help educate consumers about the consequences of overdose, the subpopulations that should not take certain drugs, the risks inherent in use of particular drugs, the indications for which particular drugs are effective, and how to take these drugs. Doing so would promote the public safety and the public interest.

As currently designed, however, the Campaign does not communicate these important messages or help consumers make wise choices. Instead it will push consumers away from taking a drug that will, for some consumers at some times, be the best drug for them to take, and encourage them to take others when it may be inappropriate.

It would be easy to recite multiple examples. But, as illustration, one example should suffice. Highlighting the dangers of acetaminophen overdose in children without even mentioning that aspirin is contraindicated for use in children in many situations because of the

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29. At the NDAC meeting, Dr. Katz urged a stronger GI warning on NSAIDs, explaining that "GI bleeds and deaths from GI bleeds in this country are a big problem. They are a much bigger problem than the acetaminophen overdoses we heard about and spent a lot of time talking about yesterday, and I think we have to take a stronger stand . . . ." Sept. 20th Transcript at 248. No one disagreed with his statement.

30. The Mediscope Household Survey shows that the overwhelming majority of consumers use analgesics within the recommended OTC dose. A small percentage of analgesic users exceed the recommended maximum daily dose; 1% for acetaminophen, 6% for ibuprofen and 13.5% for naproxen. For aspirin, 92.4% of daily usage was 1 to 2 tablets (within recommended dose), but the data may not represent usage for pain relief, inasmuch as 52% of reported usage was for the prevention of heart attack or stroke. Mediscope Household Survey at 15 (2002).

potential for Reye's Syndrome cannot be in any way objective. FDA has spent years trying to educate consumers not to use aspirin in children when the child has chicken pox or flu symptoms. Yet now it has initiated a Campaign that will push parents in exactly that direction. Especially in view of the Agency's current emphasis on pediatric populations, it is hard to understand how this could have been allowed to happen.

Conclusion

For several years, while acknowledging the very real dangers of acetaminophen overdose, McNeil has attempted to communicate with CDER officials the important adverse public health consequences of presenting an unbalanced picture of NSAID and acetaminophen risk. Now, FDA has taken a step that will make those consequences a reality. The Campaign, as currently constructed, is contrary to the requirements of the FDQA. It is also arbitrary, capricious, and an abuse of discretion in violation of the Administrative Procedure Act. In the interests of the public health, sound science and fundamental fairness, the Campaign should be corrected. McNeil asks that FDA do so, and that it process this request on an expedited basis in order to limit the damage that is being done.

Sincerely,

Nancy L. Buc
Kate C. Beardsley

Cc: Mr. Steven H. Unger
Acting Chief Mediator & Ombudsman (HF-7)

EXHIBIT A

FDA Consumer magazine
January-February 2003

U.S. Food and Drug Administration

Use Caution With Pain Relievers

Acetaminophen is a safe and effective pain reliever that benefits millions of consumers. However, taking too much could lead to serious liver damage. The drug is sold under brand names such as Tylenol and Datril, but it is also available in many cough and cold products and sleep aids, and is an ingredient in many prescription pain relievers.

In September 2002, the FDA Non-Prescription Drugs Advisory Committee discussed safety issues related to the use of pain relievers sold over-the-counter (OTC), including acetaminophen, aspirin, ibuprofen and naproxen.

Acetaminophen can cause liver injury through the production of a toxic metabolite. The body eliminates acetaminophen by changing it into substances (metabolites) that the body can easily eliminate in the stool or urine. Under certain circumstances, particularly when more acetaminophen is ingested than is recommended on the label, more of the harmful metabolite is produced than the body can easily eliminate. This harmful metabolite can seriously damage the liver.

The signs of liver disease include abnormally yellow skin and eyes (jaundice), dark urine, light-colored stools, nausea, vomiting, and loss of appetite. The signs can be similar to flu symptoms and may go unnoticed for several days if consumers believe their symptoms are related to their initial illness. Serious cases of liver disease may lead to mental confusion, coma, and death.

To avoid accidental overdosing, it's very important not to take more than the recommended dose on the label. Also, you should not take acetaminophen for more days than recommended, or take more than one drug product that contains acetaminophen at the same time. Consumers should be aware that taking more than the recommended dose will not provide more relief.

If you're taking a prescription pain medicine, check with your doctor first before taking OTC acetaminophen. The prescription pain medicine may also contain acetaminophen. Acetaminophen is also available in combination with other OTC drug ingredients. So, you need to check the labels of other OTC drug products for the ingredient. In some cases of accidental acetaminophen overdose, it appears that consumers used two or more acetaminophen-containing products at the same time.

Some individuals appear to be more susceptible to acetaminophen-induced liver toxicity than others. People who use alcohol regularly may be at increased risk for toxicity, particularly if they use more than the recommended dose. Further research needs to be conducted in alcohol users to determine what factors make some alcohol users more susceptible to liver injury than others.

Parents should be cautious when giving acetaminophen to children. For example, the infant drop formula is three times more concentrated than the children's suspension. It's important to read drug labels every time you use a drug and to know what dosage strength

you are using.

Improvements to labeling and consumer information for acetaminophen are among the recommendations made by the FDA's Nonprescription Drugs Advisory Committee. The committee recommended including the word "acetaminophen" in bold type on the labels for all drug products containing the ingredient and a warning about acetaminophen's potential to cause liver damage.

The committee also recommended that labeling for aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen include warnings about the potential for gastrointestinal bleeding that may be associated with use of these products. Aspirin is sold under brand names such as Bayer and St. Joseph's. Ibuprofen is sold under names such as Advil and Motrin. Naproxen is sold under the name Aleve. There are generic versions available for all of these products, as well.

The risk for bleeding is low for those who take these products intermittently. For those who take the products on a daily or regular basis, the risk is increased, particularly for those over 65 years of age or those who take corticosteriods (such as prednisone). Those who use hormone therapy (estrogens and progestins) for post-menopausal symptoms or birth control do not have an increased risk for bleeding.

In addition, the committee recommended adding labeling language that urges consumers to ask health care providers about NSAID use if they have kidney disease or are taking diuretics (fluid pills).

The FDA is evaluating the committee's advice and working to complete rulemaking for these OTC pain relievers/fever reducers.

FDA/Office of Public Affairs
Web page created by **tg** 2003-JAN-06.

Return to the IATROGENIC DISEASE Page

EXHIBIT B

Why is it important to know that all these medicines contain acetaminophen?

Because too much can damage your liver.

Acetaminophen is an active ingredient found in more than 600 over-the-counter and prescription medicines, such as pain relievers, cough suppressants and cold medications. It is safe and effective when used correctly, **but taking too much can lead to liver damage.** Different medicines contain different amounts, so follow dosage directions carefully. And don't take more than one acetaminophen product a day without first speaking to a health care professional. To learn more, call 1-888-INFO-FDA or visit www.fda.gov/cder.

Read the label. Know the active ingredients in your medicines.

FDA

U.S. [illegible]

The best way to take your over-the-counter pain reliever? Seriously.

Know the active ingredients in your pain relievers. Read the label.

Pain relievers such as aspirin, ibuprofen and naproxen are known as nonsteroidal anti-inflammatory [illegible] medicines are safe and effective when taken as directed [illegible] kidney problems in some people. Always read the label warnings, and follow [illegible] dosing. And be sure to talk with your health care professional or pharmacist if you have any questions. You can also learn more by calling 1-888-INFO-FDA or visiting www.fda.gov/[illegible].

FDA

U.S. Department of Health and Human Services
Food and Drug Administration

EXHIBIT C

DATE: January 22, 2004

FROM: Center for Drug Evaluation and Research
Food and Drug Administration

SUBJECT: Acetaminophen Hepatotoxicity and Nonsteroidal Anti-Inflammatory Drug (NSAID)-related Gastrointestinal and Renal Toxicity

TO: State Boards of Pharmacy

The FDA is addressing this letter to bring to your attention important safety issues for all drug products that contain acetaminophen or NSAIDs. 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.

This letter is intended to raise the awareness of pharmacists about the important educational role that they can play in preventing acetaminophen induced hepatotoxicity and NSAID-related gastrointestinal bleeding and renal toxicity in consumers using these medicines.

1. Acetaminophen Toxicity

The danger of hepatotoxicity in association with acetaminophen use has been well recognized. Acetaminophen induced hepatotoxicity is caused by a toxic metabolite of the parent compound and can lead to liver failure, which may result in liver transplant or death. The purpose of the advisory committee meeting was to review the data on unintentional overdose and determine whether additional measures should be taken to decrease the risk of these events.

Reasons for unintentional overdoses appear to be multi-factorial. Examples identified by the advisory committee included:

- The lack of consumer understanding of the potential adverse consequences of taking two different products containing acetaminophen simultaneously.
- Failure of consumers to recognize the potential harm from exceeding the recommended dose of medications.
- The wide variety of products available both OTC and by prescription that contain acetaminophen (e.g., combinations, single ingredient, multiple formulations).
- Failure of consumers to recognize the active ingredients in various combination prescription (Rx) and OTC drug products.
- Container labeling for prescription products, dispensed by a pharmacy, that may not clearly identify acetaminophen as one of the active ingredients and the maximum daily acetaminophen dose limit.

2. NSAID-related GI and Renal Toxicity

Multiple NSAIDs are available Over the Counter (OTC) (e.g., aspirin, ibuprofen, naproxen) and by prescription (ibuprofen, indomethacin, etc.). Attributable adverse events such as GI bleeding and renal toxicity associated with their use are well known. The following NSAID-related risk factors for GI bleeding were identified by the advisory committee:

- Use of concomitant medications such as anticoagulants, corticosteroids;
- concomitant use with low dose aspirin or with other NSAIDs;
- increasing age ($\geq$ 60 years);
- increasing dose;
- previous history of GI bleeding; and
- concomitant use of alcohol.

The following NSAID-related risk factors for renal toxicity were identified:

- Volume depletion;
- underlying kidney disease;
- congestive heart failure;
- elderly ($\geq$ 65 years);
- hypertension; and
- diabetes.

The advisory committee's discussions and suggestions about acetaminophen hepatotoxicity and NSAID-related GI and renal toxicity can be viewed on-line at the following FDA website:

http://www.fda.gov/ohrms/dockets/ac/cder02.htm#Nonprescription%20Drugs

The FDA believes that pharmacists are vital in any adverse event prevention effort. Pharmacists provide important information to patients and consumers regarding the appropriate use of prescription and OTC drug products. The Agency is asking that you consider the steps listed below to help ensure that patients and consumers use prescription and OTC pain relievers correctly. The following container labeling recommendations for prescription products are being submitted for your consideration:

Acetaminophen:

All prescription drugs containing acetaminophen should be adequately labeled on the container, so that all active ingredients (such as acetaminophen) and strengths appear on the prescription label. Additional recommendations for container labeling are as follows:

- Do not use drug name abbreviations, such as APAP for acetaminophen, to avoid consumer confusion.
- Include a statement instructing the patient to avoid concurrent use of any other acetaminophen containing products.
- Include a statement instructi ng the patient not to exceed the maximum daily recommended dose of acetaminophen.
- Include a statement instructing the patient to avoid alcoholic drinks while using the drug product.

NSAIDs:

We recommend that the labeling for all prescription products containing NSAIDs:

- Clearly identify that one of the ingredients in the product is an NSAID.
- Include a statement instructing the patient not to exceed the recommended single and/or daily dose.
- Include a statement instructing the patient to avoid taking any other NSAID containing products (OTC or Rx), or with products containing anticoagulants, corticosteroids, or diuretics.
- Include a statement instructing the patient to avoid alcoholic drinks while using the drug product.

FDA is reviewing various proposed changes to labeling for OTC products that contain acetaminophen and NSAIDs that will better reflect the latest scientific knowledge about the potentially serious risks associated with the use of these products. In the meantime, the FDA is planning a national educational campaign to alert U.S. consumers about the risks associated with the use of pain relievers and steps they can take to reduce these risks.

State Boards of Pharmacy regulate container labeling for prescription drugs. At present there are approximately two hundred approved new and generic combination narcotic analgesic prescription drug products that contain acetaminophen. Your assistance in addressing the container labeling requirements of prescription products that contain acetaminophen, as well as your assistance with education for both healthcare providers and consumers is essential for improving the safe use of analgesic/antipyretic drug products.

Thank you for your critically important contribution to the safety of patients taking acetaminophen and NSAID containing products.

Should you have any questions regarding this communication, please contact Dr. Charles Ganley, Director, Division of Over-the Counter Drug Products, 301-827-2222.

Sincerely,

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

EXHIBIT D

Questions and Answers on Using Over-the-Counter (OTC) Human Drug Products Containing Analgesic/Antipyretic Active Ingredients Safely

1. What is the Food and Drug Administration (FDA) announcing today?

The Agency is announcing today:

- A national consumer education campaign to help consumers understand how to safely use OTC pain relievers (analgesics) and fever reducers (antipyretics).
- The important educational role healthcare professionals can play in educating consumers in the safe use of these products.

2. What prompted this campaign?

In September 2002 FDA's Non-Prescription Advisory Committee (NDAC) held a public meeting to review the safety and labeling of certain OTC drug products such as acetaminophen, aspirin, and nonsteroidal anti-inflammatory drug (NSAIDs). Specifically, the committee reviewed cases of severe liver injury associated with the use of acetaminophen. They also reviewed cases of stomach bleeding and kidney injury related to the use of aspirin and NSAIDs. The committee recommended changes to the labels of these products to better inform consumers about the ingredients in the products and possible serious side effects with improper use. NDAC also recommended that FDA take a more active role in the education of consumers and health providers about the safe use of these products.

3. How do consumers take these medications safely?

You can take these medications safely by carefully reading the directions and by understanding what drugs are in the products you take. People can take too much acetaminophen either by not following directions or by taking products at the same time that both contain acetaminophen. Be sure and read the directions.

For NSAIDs, carefully read the label and make sure you do not have a health condition that would increase your risk. Aspirin and other NSAIDs can cause stomach bleeding. Although it is rare for these events to occur when using OTC doses and for short periods of time, some people do develop bleeding. You have an increased risk if you:

- have a previous history of stomach bleeding,
- are over the age of 60,
- drink three or more alcoholic drinks a day,
- take steroid medications, or take other NSAID medications.

4. **What does NSAID mean?**

Nonsteroidal anti-inflammatory drugs are often referred to as NSAIDs. This is a group of drugs that include products such as ibuprofen, naproxen and aspirin. NSAIDs are taken to reduce minor aches and pains, headaches and fevers.

5. **Are these pain relievers safe to use?**

Pain reliever and fever reducer drug products have been available for many years without a prescription. These products are safe and effective when used by consumers properly. The FDA believes that consumers need to know that pain relievers or fever reducers can cause serious side effects when used improperly. FDA urges people to read the labels of all the OTC medicines they take to know how to take them properly.

6. **Where can I find more information on this?**

You can find out more information by reading the FDA Consumer article "Use Caution with Pain Relievers". You can also ask your pharmacist or healthcare provider if you have questions about using OTC medicines with your prescription medicines.

If you have further questions regarding any medications, please contact the Center for Drug's Division of Drug Information at: 888-INFO.FDA (888-463-6332), or email us at: druginfo@cder.fda.gov.

Back to Top Back to Analgesics

Date created: 1/22/2004

EXHIBIT E

Before using any medicine, remember to think SAFER:

S

A

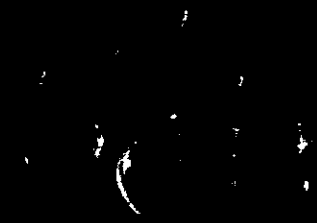
F

E

R

The best way to take your over-the-counter pain reliever?

Seriously.



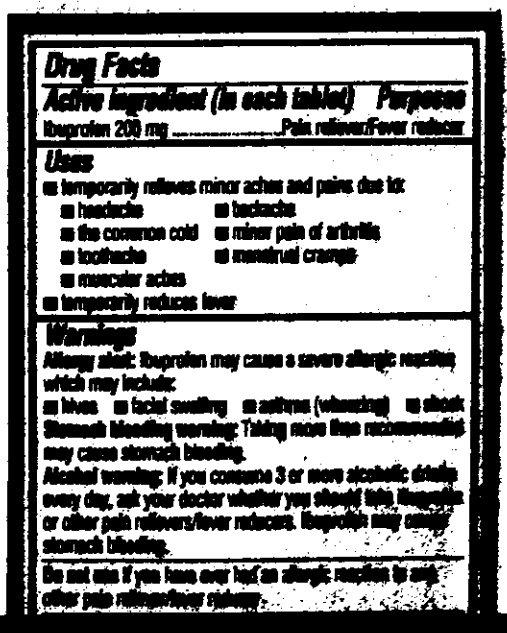
FDA

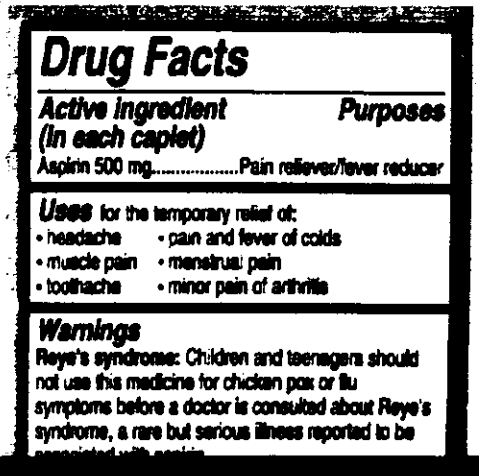
FDA

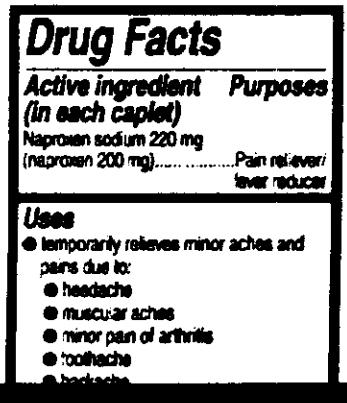
Over-the-counter (OTC) pain relievers/fever reducers (the kind you can buy without a prescription) are safe and effective when used as directed. However, they can cause serious problems when used by people with certain conditions or taking specific medicines. They can also cause problems in people who take too much, or use them for a longer period of time than the product's *Drug Facts* label recommends. That is why it is important to follow label directions carefully. If you have questions, talk to a pharmacist or health care professional.

What are pain relievers/ fever reducers?

There are two categories of over-the-counter pain relievers/fever reducers: acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs). Acetaminophen is used to relieve headaches, muscle aches and fever. It is also found in many other medicines, such as cough syrup and cold and sinus medicines. OTC NSAIDs are used to help relieve pain and reduce fever. NSAIDs include aspirin, naproxen, ketoprofen and ibuprofen, and are also found in many medicines taken for colds, sinus pressure and allergies.







How do I use pain relievers/ fever reducers safely?

These products, when used occasionally and taken as directed, are safe and effective. Read the labels of all your over-the-counter medicines so you are aware of the correct recommended dosage. If a measuring tool is provided with your medicine, use it as directed.

What can happen if I do not use pain relievers/fever reducers correctly?

Using too much acetaminophen can cause serious liver damage, which may not be noticed for several days. NSAIDs, for some people with certain medical problems, can lead to the development of stomach bleeding and kidney disease.

What if I need to take more than one medicine?

There are many OTC medicines that contain the same active ingredient. If you take several medicines that happen to contain the same active ingredient, for example a pain reliever along with a cough-cold-fever medicine, you might be taking two times the normal dose and not know it. So read the label and avoid taking multiple medicines that contain the same active ingredient or talk to your pharmacist or health care professional.

EXHIBIT F

FDA News

FOR IMMEDIATE RELEASE
P04-04
January 22, 2004

Media Inquiries: 301-827-6242
Consumer Inquiries: 888-INFO-FDA

FDA Launches Consumer Campaign on Safe Use of OTC Pain Products

The Food and Drug Administration (FDA) today launched a national education campaign to provide advice on the safe use of over-the-counter (OTC) pain relief products.

"Pain relievers and fever reducers are safe drugs when used as directed, but they can cause serious problems when used by people with certain conditions or those who are taking specific medicines," said FDA Commissioner Mark B. McClellan, M.D., Ph.D. "We want to remind consumers who take these products that it's important to follow current dosing and label directions carefully."

FDA's nationwide campaign focuses on the OTC pain and fever reducers that contain acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs), which include products such as aspirin, ibuprofen, naproxen sodium and ketoprofen.

"'Read labels carefully, be sure you are getting the proper dose, and check with your doctor or pharmacist to be sure that you can use these drugs safely," said Dr. McClellan.

Many OTC medicines sold for different uses have the same active ingredient. For example, a cold-and-cough remedy may have the same active ingredient as a headache remedy or a prescription pain-reliever. To minimize the risks of an accidental overdose, consumers should avoid taking multiple medications that contain the same active ingredient at the same time.

Acetaminophen is an active ingredient found in more than 600 OTC and prescription medicines, such as pain relievers, cough suppressants and cold medications. It is safe and effective when used correctly, but taking too much can lead to liver damage, and even death. The risk for liver damage may be increased in consumers who drink three or more alcoholic beverages per day while using acetaminophen-containing medicines.

NSAIDs are common pain relievers that are also used to relieve fever and minor aches and pains. Examples of NSAIDs are aspirin, ibuprofen, naproxen sodium, and ketoprofen. These products can cause stomach bleeding with an increased risk in consumers who are over 60, are taking prescription blood thinners, are taking steroids or have a history of stomach bleeding. NSAIDS may also increase the risk of reversible kidney problems in consumers with preexisting kidney disease, or who are taking a diuretic (water pill).

The FDA's consumer educational campaign will include: 1) an OTC pain reliever brochure to be distributed in pharmacies, and by health care providers, 2) a "matte release" newspaper article to be distributed to 10,000 community papers across the country, 3) a reprint of "Use Caution With Pain Relievers", an *FDA Consumer* magazine article that will be distributed at national healthcare conferences and available for reprinting in health related publications and 4) two print public service ads that will be sent to approximately 100 major magazines. All of these materials are available on the web at http://www.fda.gov/cder/drug/analgesics/default.htm.

The campaign will provide advice on how to avoid inadvertently taking more than the recommended doses of these medicines and outline underlying health conditions that increase risk.

In September 2002, FDA's Non-Prescription Drugs Advisory Committee recommended changes to labeling of certain OTC drug products, including acetaminophen and NSAIDS. They advised that these changes are needed to better inform consumers about the ingredients in these products and possible side effects caused by improper use. In addition to this new consumer outreach effort, FDA will consider changing the labeling of these products to further bolster their safe use. FDA is reviewing various changes to labeling for these ingredients that better reflect the latest scientific knowledge about OTC oral pain relievers.

The FDA recommends that consumers talk with healthcare professionals or pharmacists if they have questions about using an OTC medicine and especially before using them in combination with dietary supplements or OTC or prescription medicines. To learn more, call 1-888-INFO-FDA or visit www.fda.gov/cder.

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EXHIBIT G

Food and Drug Administration
Science Background

Safety Concerns Associated with Over-the-Counter Drug Products Containing Analgesic/Antipyretic Active Ingredients for Internal Use

January 22, 2004

This Science Paper is intended to raise the awareness of healthcare professionals about the important educational role that they can play in preventing unintentional acetaminophen induced hepatotoxicity and NSAID-related gastrointestinal bleeding and renal toxicity in their adult and pediatric patients. The FDA Nonprescription Advisory Committee (NDAC) reviewed safety data related to the use of these pain relievers on September 19-20, 2002, and made recommendations regarding ways to better educate patients and consumers in order to reduce the risk of these rare, but potentially serious adverse events. [1]

History

Acetaminophen has been marketed in the United States as an over-the-counter (OTC) antipyretic/analgesic agent since 1960. It is widely available in a variety of strengths and formulations for children and adults as a single-ingredient product, and can also be found in numerous combination OTC and prescription drug products.

Chemically acetaminophen is a para-aminophenol derivative that is also the active metabolite of the analgesic drug phenacetin. [2] Its effectiveness as an antipyretic agent has been attributed to its effect on the hypothalamic heat center, while its analgesic efficacy is due to its ability to raise the pain threshold. [2]

Acetaminophen's ability to cause fulminant hepatic failure in acute intentional overdose situations or when used in combination with alcohol is well known. The latter resulted in the addition of an alcohol warning on all OTC acetaminophen-containing products since 1998. An internal review of post-marketing case reports collected by the FDA's Adverse Event Reporting System (AERS) identified 307 cases of hepatoxicity in both adults and children during the period from January 1998 to July 2001, where at least one acetaminophen containing product was considered to be a suspect drug. The agency review focused on cases of unintentional overdose (not related to a suicide attempt) of acetaminophen leading to hepatotoxicity. The agency also reviewed data from liver failure transplant lists and other information submitted to the agency. Many of these cases are consistent with published reports in the worldwide literature, and provided the basis for public discussion of the drug's safety profile at the September 2002 NDAC meeting.

NSAIDs include aspirin, which irreversibly acetylates cyclooxygenase (COX), and several other classes of organic acids, including propionic acid derivatives (ibuprofen, naproxen, etc.), acetic acid derivatives (indomethacin, etc.), and enolic acid acids (e.g., piroxicam), all of which are reversible competitors with arachidonic acid at the active site of cyclooxygenase [3]. There are two forms of cyclooxygenase, COX-1 found in blood vessels, stomach and kidney, and COX-2, which is induced in settings of inflammation by cytokines and inflammatory mediators. All currently available OTC NSAIDs are non-selective COX inhibitors. The antipyretic, analgesic, and antiinflammatory actions of NSAIDs are related to their ability to inhibit COX-2. Side effects such as gastrointestinal (GI) bleeding and renal toxicity are a result of the inhibition of COX-1 and are well-known complications of NSAID therapy [3,4,5].

Review of post-marketing case reports collected by the FDA's Adverse Event Reporting System (AERS) between 1998 and 2001 identified a total of 279 cases of GI bleeding associated with the OTC use of NSAIDs: 197 cases for ibuprofen, ketoprofen and naproxen, and 82 cases for aspirin. The cases were screened for the use of these analgesic products, or for mention of OTC use in the narrative of the report. These reports are consistent with published case studies from the worldwide literature.

Data supporting a nephrotoxic risk associated with use of OTC NSAIDs was compiled from adverse events reported to the FDA's AERS database and large population studies. Cases of acute renal failure with the use of OTC NSAIDs are rare. Individuals with conditions where renal perfusion is more dependent on prostaglandins (e.g. congestive heart failure, hepatic cirrhosis with ascitis, chronic renal disease, or hypovolemia such as occurs with dehydration) are at particular risk for acute renal failure.

Considering the wide spread use of OTC analgesic/antipyretic drug products, the FDA acknowledges that the serious adverse event rate is low. However, it is clear that many of the serious adverse events are preventable.

What are the factors that contribute to these cases?

Acetaminophen Hepatotoxicty

The acetaminophen safety review update identified four factors, which have resulted in potentially fatal or life threatening unintentional overdoses in the adults:

- failure by consumers to recognize the ingredients contained in OTC drug products and/or the potential for harm due to exceeding the recommended dose
- the wide variety and availability of both OTC and prescription drug products that contain acetaminophen (e.g., single ingredient, combinations, and multiple formulations)
- the lack of consumer awareness for the potential to develop serious adverse events from taking two or more different products containing acetaminophen concomitantly
- the failure of prescription container labels to list acetaminophen as an ingredient

Four situations were identified which resulted in unintentional overdoses in children:

- administering the **wrong** pediatric acetaminophen formulation [i.e., substituting the concentrated infant drops (80mg/0.8ml) for the less concentrated children's suspension (160 mg/5 ml)]
- administering the adult instead of the age-appropriate children's formulation
- incorrectly calculating the weight-appropriate dose of acetaminophen
- using the wrong dosing device (e.g., tablespoon instead of teaspoon, dropper versus syringe)

NSAIDs Gastrointestinal Bleeding and Renal Toxicity
The NSAID safety data review identified the following risk factors for GI bleeding for OTC and prescription NSAIDs:

- use of concomitant medications such as anticoagulants and/or corticosteroids
- concomitant use of low dose aspirin and other NSAIDs
- increasing age ($\geq$ 60 years)
- increasing dose
- previous history of GI bleeding
- concomitant use of alcohol

The following at-risk populations for NSAID-induced nephrotoxicity were identified:

- patients with volume depletion
- underlying kidney disease
- congestive heart failure
- elderly ($\geq$ 65 years)
- hypertension
- diabetes

Discussion
The unintentional acetaminophen overdoses resulting in liver failure, and the cases of GI bleeding and renal toxicity attributable to the use of OTC NSAIDs underscore the need for better consumer education about which products contain acetaminophen or an NSAID and conditions for safe product use. Many of these adverse events are preventable. Consumers need to recognize that serious health consequences can result from unsafe use of over-the-counter analgesics.

Recommendations
Health care providers should prescribe adequate pain medication regimens for patients and provide instructions regarding the use of other pain medications, including appropriate warnings about use of multiple and combination products containing the same active ingredient. The FDA encourages healthcare providers to help prevent the morbidity and mortality of acetaminophen-induced hepatotoxicity and NSAID-related GI and renal effects by educating their patients about the following:

- that **any OTC analgesic** is a drug and appropriate safety precautions need to be taken when using or storing it

- the wide variety of different strengths, formulations, and combinations of acetaminophen- and NSAID-containing products that are available OTC and by prescription
- the correct dosing frequency for each of the acetaminophen or the NSAID formulations
- the correct weight-based dose for each child
- the use of the correct measuring device for liquid formulations
- drinking more than 3 alcoholic drinks every day is not compatible with safe acetaminophen or NSAID use
- risks of taking OTC analgesics with other prescription or non-prescription medications
- signs and symptoms of self-recognizable side effects
- the potential problems associated with using more than one pain reliever product simultaneously

The FDA is also recommending that all U.S. Boards of Pharmacy implement changes to the container labeling for all prescription drugs containing acetaminophen or NSAIDs so that all active ingredients (such as acetaminophen or NSAID), their strengths, recommended single and daily dose, and warnings appear on the prescription label.

Most importantly health care professionals should remind their patients to always read their OTC and prescription medication labels and carefully follow the directions.

References

[1] Nonprescription Drug Advisory Committee Meeting, September 2002 transcripts located at www.fda.gov/ohrms/dockets/ac/02/transcripts/3882T1.htm

[2] Woodbury DM, Fingl E: Analgesic-Antipyretic and Antiinflammatory Agents and Drugs Employed in the Treatment of Gout. *In* Hardman JG, Gilman AG, Limbird LE (eds): Goodman's &Gilman's The Pharmaceutical Basis of Therapeutics, 5th ed. New York, Mcgraw-Hill, 1970: 325-58

[3] Insel P: Analgesic-Antipyretic and Antiinflammatory Agents and Drugs Employed in the Treatment of Gout. *In* Hardman JG, Gilman AG, Limbird LE (eds): Goodman's &Gilman's The Pharmaceutical Basis of Therapeutics, 5th ed. New York, Mcgraw-Hill, 1996: 617-43

[4] Lanza FL, et al: A guideline for treatment and prevention of NSAID-induced ulcers. Am J Gastroenterol 1998; 93(11):2037-46

[5] Altman RD, et al: Recommendations for the medical management of osteoarthritis of the hip and knee; 2000 update. Arthritis Rheum 2000; 43(9): 1905-15

EXHIBIT H

Health Hints: Use Caution with Pain Relievers

(NAPS) -- Pain relievers, when used correctly, are safe and effective. Millions of people use these medicines everyday. Not using them according to the label directions can have serious consequences.

The U.S. Food and Drug Administration (FDA) wants you to benefit from your medicines and not be hurt by them. You should know the active ingredients and directions of all your medicines before you use them.

Over-the-counter (OTC) medicines list all their active ingredients on the package. For prescription drugs, the leaflet that comes with your prescription lists the active ingredients contained in the medicine.

Many OTC medicines sold for different uses have the same active ingredient. Also, active ingredients in OTC medicines can be ingredients in prescription medicines. For example, a cold-and-cough remedy may have the same active ingredient as a headache remedy or a prescription pain reliever.

There are basically two types of OTC pain relievers. Some contain acetaminophen and others contain non-steroidal anti-inflammatory drugs (NSAIDs). These medicines are used to relieve the minor aches and pains associated with:

- headaches
- colds
- flu
- arthritis
- toothaches
- menstrual cramps

These medicines are also used to treat migraine headaches, and to reduce fever.

Acetaminophen is a very common pain reliever and fever reducer. Taking too much of this active ingredient can lead to liver damage. The risk for liver damage may be increased if you drink three or more alcoholic drinks while using acetaminophen-containing medicines.

NSAIDs are common pain relievers and fever reducers. Examples of OTC NSAIDs are aspirin, ibuprofen, naproxen sodium, and ketoprofen. There are some factors that can increase your risk for stomach bleeding:

- if you are over 60
- taking prescription blood thinners
- have previous stomach ulcers or
- other bleeding problems

If you have any of these factors, you should talk to your Doctor before using NSAIDS.

NSAIDs can also cause reversible damage to the kidneys. The risk of kidney damage may increase in:

- people who are over 60
- people who have high blood pressure, heart disease or pre-existing kidney disease
- people who are taking a diuretic

The FDA recommends that you talk with your healthcare professional if you have questions about using an OTC medicine before using it in combination with other medicines -- either OTC or prescription medicine.

You can learn more about what medicines are right for you by reading the label carefully and talking to your healthcare professional or pharmacist.

For more information, visit http://www.fda.gov or call 1-888-INFOFDA.

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Date created: January 22, 2004

EXHIBIT I

McNeil
Consumer & Specialty Pharmaceuticals

SEP 0 3 2002

Sandra Titus, Ph.D.
Advisors and Consultants Staff (HFD-021)
FDA/Center for Drug Evaluation and Research
5630 Fishers Lane
Rockville, MD . 20857

Re: Background Package - McNeil Consumer & Specialty Pharmaceuticals
September 20, 2002 - Nonprescription Drugs Advisory Committee (NDAC)
OPEN NSAIDS

Dear Dr. Titus:

Attached is McNeil's background package on aspirin and other OTC NSAIDs for the September 20, 2002 meeting of the Nonprescription Drugs Advisory Committee.

This material is available for public disclosure without redaction.

If you have any questions, or need additional information, please contact me at 215-273-7878.

Very truly yours,

Paula J. Oliver

Paula J. Oliver
Senior Director
Medical & Regulatory Science

Attachments

PJO0735.DOC

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1 INTRODUCTION

McNeil Consumer & Specialty Pharmaceuticals (McNeil), a member of the Johnson & Johnson family of companies, submits this background package for the Nonprescription Drugs Advisory Committee (NDAC) meeting scheduled for September 20, 2002.

McNeil markets St. Joseph® low strength (81 mg) aspirin that is intended for use by adults only. In addition, McNeil markets Motrin® (ibuprofen) and Tylenol® (acetaminophen) single-ingredient and combination-ingredient adult and pediatric products.

McNeil's submission provides data and an evidence-based assessment of the safety of aspirin and other OTC-available NSAIDs.

KEY POINTS

- The risk of aspirin and other NSAID-related gastrointestinal effects occurs at recommended doses and is dose-related.
- Salicylate poisoning, particularly chronic salicylism, has a high risk of mortality despite treatment.
- At OTC recommended doses, ibuprofen appears to have the least risk of gastrointestinal toxicity when compared to other NSAIDs.
- Medication use surveys provide insight regarding consumer behaviors that may result in excessive OTC analgesic exposure.

- McNeil has implemented labeling and educational interventions aimed at focusing the attention of OTC medication users on:
  - the product ingredients
  - the proper dosing and proper use of medications
  - the importance of not taking more than the recommended dose
  - the importance of not using two products containing identical ingredients or using the same class of analgesic ingredients (eg, NSAIDs) during the same period of time
  - the importance of recognizing that all medications have risks, particularly when more than the recommended dose is taken.

- If acetaminophen use were to be restricted, and consequently aspirin and other OTC NSAID use increased in the United States, available data suggest that more people would die from aspirin and other NSAID-related gastrointestinal bleeding than those potentially spared from acetaminophen overdose hepatotoxicity.

2 ASSESSMENT OF SAFETY OF ASPIRIN AND OTHER NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

KEY POINTS

- Consumers will self-treat pain and their selection of OTC analgesics will depend on availability, accessibility, and effectiveness of these products.
- The risk of aspirin and other NSAID-related gastrointestinal effects occurs at recommended doses and is dose-related.
- Salicylate poisoning, particularly chronic salicylism, has a high risk of mortality despite treatment.
- At OTC recommended doses, ibuprofen appears to have the least risk of gastrointestinal toxicity when compared to other NSAIDs.
- If acetaminophen use were to be restricted, and consequently aspirin and other OTC NSAID use increased in the United States, available data suggest that more people would die from aspirin and other NSAID-related gastrointestinal bleeding than those potentially spared from acetaminophen overdose hepatotoxicity.

2.1 Exposure Data of Aspirin and Other NSAIDs

Aspirin and other OTC NSAIDs are widely used throughout the United States. A recent survey of medication use in the United States reported that ibuprofen was taken by 17% of adults, aspirin was taken by 17% of adults, and naproxen was taken by 3.5% of adults in the preceding week [Kaufman 2002]. Based on market data provided by Information Resources, Inc., it is estimated that in the year 2001, approximately 14.5 billion tablets of OTC single-ingredient aspirin, 12.7 billion tablets of OTC single-ingredient adult ibuprofen, 2.8 billion tablets of OTC adult naproxen sodium and 55 million tablets of OTC adult ketoprofen were purchased.

2.2 Mechanism of Action

Nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin act by inhibiting prostaglandin G/H synthase isoenzymes, also known as cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). These isoenzymes are responsible for the conversion of arachidonic acid to various tissue specific prostaglandins and thromboxanes [FitzGerald 2001; McGeehan 2002]. COX-1 is constitutively expressed in all tissues and is responsible for generating prostaglandins that maintain organ function, protect the integrity of the gastric mucosa and generate platelet-derived thromboxane responsible for platelet aggregation and vasoconstriction [Konstam 2001; Bjorkman 2002]. During the inflammatory process COX-2 is induced, generating prostaglandins that mediate pain and inflammation [Bombardier 2000]. COX-2 is also present constitutively in the kidneys and vascular endothelium [Hillis 2002]. Reported adverse experiences with aspirin and other NSAIDs can be understood on the basis of this mechanism of action.

2.3 Prior FDA Findings of Adverse Events

The agency has published a final rule for professional labeling of aspirin that highlights concerns that may occur with use of aspirin, and a proposed monograph for ibuprofen that outlines reasoning behind proposed labeling changes.

The FDA notice of final rule making (Final Rule) published in the Federal Register of October 23, 1998 (63 FR 56816) regarding professional labeling for aspirin describes adverse experiences that include, but are not limited to, renal insufficiency and failure, prolonged prothrombin time, acute anaphylaxis, and asthma. Various drug interactions are noted and general precautions include renal failure, hepatic insufficiency, and patients on a

sodium-restricted diet (eg, patients with congestive heart failure). Signs/symptoms and management of overdose are also described.

The FDA published a notice of proposed rule making (Proposed Rule) in the Federal Register of August 21, 2002 (67 FR 54152) regarding ibuprofen. Proposed labeling changes include, but are not limited to, an asthma/allergy warning and other warnings that advise individuals to ask their doctor if they have gastrointestinal, hematologic, or renal disorders, or take an anticoagulant, diuretic or another analgesic/antipyretic. In addition, individuals with hypertension or other cardiorenal disease or those who are age 65 years or older would be instructed to consult with a physician before using the product.

In these documents, the agency provides a lengthy list of publications and literature review to substantiate these labeling changes.

2.4 Review of Gastrointestinal Adverse Events at Recommended Doses

The recommended OTC dose for aspirin is up to 4000 mg/day; for ibuprofen, up to 1200 mg/day; for naproxen sodium, up to 660 mg/day; and for ketoprofen, up to 75 mg/day. Most evaluations of NSAID risks involve prescription products or prescription doses and, therefore, probably overestimate risks associated with OTC NSAID use. Some consumers take more than the recommended daily doses of OTC NSAIDs [Havey 2001]. Singh [1999] noted that 40% of Americans (who had taken NSAIDs at least twice in the past year for five or more consecutive days) simultaneously used OTC and prescription NSAIDs. Based on consumer survey responses [Kaufman 2002], and taking into account concurrent use of two or more NSAIDs [Slone 2001], the one-week prevalence of aspirin and all other NSAID use is estimated as approximately 34%. This represents 71 million adults (0.34 x 209 million adults in the United States) [US Census Bureau 2000]. Concurrent use of two or more NSAIDs was reported by 2.7% of all adults in the Slone Survey of Analgesic Use [Slone 2001]. Applying this rate to the adult population in the United States provides an estimate of up to 5.6 million adults who may concurrently use two or more NSAIDs. These concurrent users will be at higher risk for dose-related side effects.

2.4.1 Gastrointestinal Effects at Recommended Doses

Aspirin and other NSAIDs are associated with a variety of gastrointestinal effects ranging from mild gastrointestinal discomfort (such as dyspepsia, heartburn, nausea, and abdominal pain) to more severe complications, such as gastrointestinal bleeding and

ulcers. The great majority of excess mortality in users of NSAIDs is attributable to gastrointestinal bleeding [Report of CIOMS Working Group IV 1998]. These effects are a result of primarily two mechanisms. The first mechanism involves direct local damage to the gastric mucosa, which is especially seen with acidic NSAIDs that are un-ionized in the stomach (aspirin and the propionic acid derivatives; ibuprofen, naproxen and ketoprofen). The second mechanism is the result of the inhibition of cyclooxygenase with the subsequent inhibition of the synthesis of the protective prostaglandins in the gastrointestinal mucosa [Dajani 1998]. In addition, aspirin irreversibly inhibits the formation of thromboxane A_2 in platelets [Hardman 2001], which may contribute to aspirin-related gastrointestinal bleeding.

2.4.1.1 NSAIDs in General

Evidence indicates that the gastrointestinal side effects of aspirin and other NSAIDs are dose-related [Griffin 1991; Blot 2000]. Ofman and colleagues [2002] conducted an extensive meta-analysis of severe upper gastrointestinal complications from NSAIDs. They estimated the risk of upper gastrointestinal complications (perforations, ulcers and bleeds) using data from several study designs, concluding that findings from the cohort designs were the least biased. The pooled relative risk (RR) from nine cohort studies, comprising over 750,000 person-years of exposure was 2.7 (95% CI: 2.1, 3.5).

Griffin and colleagues [Griffin 1991] evaluated the risk of peptic ulcer disease associated with the use of NSAIDs in patients 65 years of age and older. They found a dose-related effect for peptic ulcer disease increasing from a RR of 2.8 (95% CI: 1.8, 4.3) for the lowest dose to a RR of 8.0 (95% CI: 4.4, 14.8) for the highest dose category (doses not specified). Blot and McLaughlin [Blot 2000] conducted an independent analysis of case-control data from a study conducted by the American College of Gastroenterology. The risk of gastrointestinal bleeding increased two- to three-fold among recent users of aspirin, ibuprofen and other NSAIDs at OTC doses, and the risk was also dose-related. Additionally, Blot and McLaughlin reviewed seven epidemiologic studies that looked at gastrointestinal bleeding risk associated with aspirin and other NSAIDs at OTC doses (eg, 3900 mg/day for aspirin and 1200 mg/day for ibuprofen). They reported about a two-fold excess risk of gastrointestinal complications at doses lower than the maximum recommended OTC dosage, with four-fold increases at doses near the maximum, and an increase of six-fold or more at doses higher than the recommended daily dose on OTC labels [Blot 2000].

2.4.1.2 Aspirin

Adverse gastrointestinal effects are a well known risk associated with the use of aspirin, including low-dose aspirin [Kurata 1990; Laporte 1991; Levy 1988] and appear to be dose-related [Prichard 1987; Weil 1995]. The United Kingdom-transient ischemic attack (TIA) aspirin trial [UK-TIA Study Group 1991], a randomized, double-blind, placebo-controlled trial, compared aspirin doses of 300 mg/day (once daily) and 1200 mg/day (600 mg twice daily) with placebo in 2435 patients (following a recent TIA or minor ischemic stroke) with a mean follow-up of about four years. There was a dose-related increase in gastrointestinal hemorrhage with 3% and 5% of the patients assigned to 300 mg of aspirin and 1200 mg of aspirin, respectively, reporting gastrointestinal hemorrhage compared with 1% of placebo patients.

Weil et al [1995] evaluated the risk for peptic ulcer with prophylactic aspirin therapy at doses of 75 mg, 150 mg, and 300 mg daily and reported odds ratios (OR) that increased with daily dose: 2.3 (95% CI: 1.2, 4.4) for 75 mg, 3.2 (95% CI: 1.7, 6.5) for 150 mg, and 3.9 (95% CI: 2.5, 6.3) for 300 mg. Prichard and colleagues [1987] observed a significant increase in gastric mucosal bleeding from baseline with a daily aspirin dose of 75 mg, which increased two-fold at a dose of 300 mg daily (when compared with 75 mg) and increased more than five-fold at a dose of 1.8 grams/day (when compared with 75 mg).

Derry and Loke [Derry 2000] conducted a meta-analysis of 24 randomized controlled trials that evaluated almost 66,000 patients. They specifically evaluated the effect of aspirin dose and formulation on the occurrence of gastrointestinal hemorrhage. Gastrointestinal hemorrhage occurred in 2.47% of patients taking aspirin compared with 1.42% of patients taking placebo (OR 1.68; 95% CI: 1.51, 1.88; $p<0.0001$). In a separate analysis of eight trials using aspirin at doses of 50 to 162.5 mg per day, gastrointestinal hemorrhage occurred in 2.30% of patients taking aspirin compared with 1.45% of patients taking placebo (OR 1.59; 95% CI: 1.40, 1.81; $p<0.0001$).

In a case-control study involving 550 incident cases of upper gastrointestinal bleeding and 1202 population controls [Kelly 1996], a statistically significant increased risk (estimated RR ranging from 2.6 to 3.1, depending on aspirin formulation, ie, plain, enteric-coated, or buffered) of upper gastrointestinal bleeding was reported for patients regularly taking $\leq$325 mg/day of aspirin. An even greater increased risk (5.8- to 7.0-fold) of upper gastrointestinal bleeding was associated with regular intake of aspirin at doses above 325 mg/day.

2.4.1.3 Concurrent Aspirin and other NSAID Use Further Increases the Risk of Gastrointestinal Complications

The risk of gastrointestinal bleeding appears to be doubled or greater when aspirin is taken concurrently with other NSAIDs. Sorensen and colleagues [2000] studied a cohort in Denmark and evaluated the risk of hospitalization for upper gastrointestinal bleeding with the use of low dose aspirin (≤150 mg daily) in 27,694 patients. The standardized incidence rate ratio (the ratio of the observed to the expected number of upper gastrointestinal bleeding cases) for upper gastrointestinal bleeding among users of uncoated low dose aspirin was 2.6 (95% CI: 1.8, 3.5) and for coated aspirin use was 2.6 (95% CI: 2.2, 3.0). More importantly, however, Sorensen et al found that this rate ratio of upper gastrointestinal bleeding increased to 5.6 (95% CI: 4.4, 7.0) when aspirin was used concurrently with other NSAIDs. As the United States population ages and the prophylactic use of aspirin for cardiovascular protection increases, the inherent gastrointestinal risks of aspirin could be compounded by concurrent NSAID use resulting in a dose-related increase in risk.

2.4.1.4 Ibuprofen

At recommended OTC doses, ibuprofen appears to have a lower risk of gastrointestinal adverse effects compared with aspirin and other NSAIDs [Henry 1996; Straus 2001; Gutthann 1997; Garcia Rodriguez 1998]. In recent meta-analyses evaluating the occurrence of gastrointestinal complications [Henry 1996; Straus 2001], ibuprofen was reported to be the safest of all NSAIDs studied. The crude risk ratios of the other NSAIDs (including aspirin) that were evaluated ranged up to approximately four-fold higher than ibuprofen. Henry and colleagues [Henry 1996] noted that adverse gastrointestinal effects for several of the NSAIDs were dose-related. Low dose ibuprofen (≤ 1200 mg) was associated with a pooled RR of 1.6 (95% CI: 0.8, 3.2) compared with a pooled RR of 4.2 (95% CI: 1.8, 9.8) for higher dose ibuprofen (≥ 2400 mg). In another study, Gutthann et al [1997] estimated the risk of complicated ulcer for NSAID users and non-users and found that compared to users of other NSAIDs, ibuprofen users had the lowest risk of peptic ulcer (odds ratio, 2.1; 95% CI: 1.1, 4.0).

2.5 Safety of Aspirin and Other NSAIDs in Overdose

The sections that follow review data on the safety of aspirin and other NSAIDs in overdose. Fatality reports from the American Association of Poison Control Centers (AAPCC) are also provided. These data indicate that ibuprofen in overdose is relatively benign and requires

supportive and symptomatic treatment. However, acute overdose with aspirin and chronic aspirin toxicity (eg, salicylism) are associated with significant morbidity and mortality.

2.5.1 Aspirin Overdose

A 16% morbidity rate and a 1% mortality rate are reported with acute aspirin overdose [Kreplick 2001]. Although acute overdose and chronic salicylism present similarly [Woolley 1977], chronic salicylism is associated with mortality as high as 25% [Kreplick 2001]. Chronic salicylism usually occurs in the course of therapeutic use of aspirin, when an individual increases the dose and, unknowingly, saturates the biotransformation and elimination pathways [Proudfoot 1983]. As a result, a small increase in dose can produce a disproportionate increase in plasma salicylate levels. This can lead to progressive signs of salicylate intoxication including headache, tinnitus, and confusion followed by metabolic acidosis and, ultimately, coma, cardiovascular collapse, and death [Hardman 2001]. There is no antidote for salicylate poisoning and treatment is directed at decreasing absorption, increasing elimination, and supportive care [Woolley 1977; Dargan 2002].

2.5.2 NSAID Overdose

Symptoms of NSAID overdose are usually mild (eg, gastrointestinal upset, abdominal pain, vomiting and diarrhea), requiring only supportive measures; however, 5% to 10% of patients experience convulsions. Metabolic acidosis is uncommon and is usually associated with large ingestions. Very rarely, coma, prolonged seizures, apnea, bradycardia, renal failure and death occur [Jones 2002].

2.5.3 American Association of Poison Control Centers (AAPCC) Reports of NSAID Exposures

The AAPCC Toxic Exposure Surveillance System (TESS) database includes reports of human exposures to various substances (eg, pharmaceutical products, cleaning substances, chemicals, foods, and plants) submitted by poison control centers [Litovitz 2001] across the United States. In the database, an exposure is defined as a contact to the poison control center regarding administration of, or contact with a substance, but does necessarily involve toxicity. Reports are received from consumers and health care professionals via telephone. Callers typically request advice and treatment recommendations.

Call information is not verified or clarified by medical record review or other means. With respect to fatality case reports, poison control centers provide no causality probability or assessment that the reported substance(s) contributed directly or indirectly to the fatal outcome. Nevertheless, TESS is the largest single data set of reported acetaminophen exposures, and a review of recent data provides a broad perspective.

According to the AAPCC annual report [Litovitz 2001], 52 deaths involving single-ingredient aspirin were reported in the year 2000, representing a mortality rate of 0.5% (based on the number of exposures in which the outcome was known). Twenty-five percent (25%) of patients where the outcome was known experienced moderate or major effects. Table 2-1 provides a summary of aspirin and ibuprofen exposure data, based on the AAPCC 2000 annual report [Litovitz 2001]. Deaths were much fewer with ibuprofen (n= 5), although total ibuprofen exposures were reported approximately three times more often.

Table 2-1. Aspirin and Ibuprofen Exposure Data Based on the AAPCC 2000 Annual Report

		Age in Years (%)[a]			Reason for exposure (%)[b]		Outcome (%)[c]	
Product	Total Exposures	<6	6-19	>19	Unintentional	Intentional	Major	Death
Aspirin alone	16,649							
Adult formulation	5,283	31.6	32.6	35.8	49.8	47.9	1.4	0.4 n=13
Pediatric formulation	589	74.5	15.0	10.5	90.3	8.0	0	0 n=0
Unknown formulation	10,777	19.1	36.2	44.7	35.4	62.7	3.6	0.6 n=39
Ibuprofen	57,876	57.3	21.6	21.1	71.4	26.9	1.0	0.02 n=5

a: Age – expressed as % of all exposures in which the age was known for each formulation.
b: Reason for exposure – expressed as % of all exposure cases in which the reason was known for each formulation.
c: Outcome – expressed as % of all exposures cases with a known outcome for each formulation.

2.6 Comparative Safety Analysis of OTC Available Analgesics

Acetaminophen is the most commonly used OTC analgesic and any actions that effectively limit its use, or the availability of optimal dosages that are currently available, may increase the use of aspirin, other OTC NSAIDs and prescription analgesics, among other pain and fever treatments. Comparing acetaminophen safety to that of aspirin and other NSAIDs at recommended doses suggests that an increase in aspirin and other NSAID use could increase the overall morbidity and mortality associated with therapeutic OTC analgesic use. The potential public health impact for the American consumer merits consideration.

For perspective, excess mortality from gastrointestinal bleeding, the factor that dominates the overall risk profile of aspirin and other NSAIDs, that occurs at recommended doses and is dose-related, is compared with excess mortality from hepatotoxicity from overdose with acetaminophen in the following sections.

2.6.1 Excess Mortality from Gastrointestinal Bleeding Associated with NSAIDs in the United States

Epidemiologic evidence suggests that 99% of the excess mortality from NSAID use was attributable to gastrointestinal complications [Report of CIOMS Working Group IV 1998]. Annually, 1% to 2% of people taking NSAIDs on a regular basis experience serious gastrointestinal complications that result in hospitalization [Singh 2000]. Estimates of the number of deaths from NSAID-related gastrointestinal bleeding vary widely.

Singh [2000] estimated that 103,000 individuals are hospitalized annually in the United States for NSAID-related serious gastrointestinal complications at a cost in excess of two billion dollars. In addition, Singh [2000] estimated that 16,500 NSAID-related deaths occur each year in the United States among patients with rheumatoid arthritis and osteoarthritis. Presumably, these estimates are based primarily on prescription NSAIDs used for longer time periods than the OTC label recommends, but as noted earlier, some individuals may use OTC NSAIDs in excess of the OTC recommended dose or take two or more OTC NSAIDs concurrently.

A more conservative estimate came from Blot and McLaughlin [personal communication McLaughlin 2001] who estimated that 9400 Americans, age 25 years or older, die from upper gastrointestinal bleeding per year. This is based on United States mortality data from the National Center for Health Statistics from 1990 through 1999[1].

Using the pooled relative risk of upper gastrointestinal bleeding from cohort studies determined by Ofman [Ofman 2002] of 2.7 (95% CI: 2.1, 3.5), McNeil estimated that the number of excess deaths per year from gastrointestinal bleeding secondary to NSAID use among adults in the United States is 3443 (95% CI; 2559, 4319). The point estimate of the number of excess deaths was calculated as follows. Estimates for the upper and lower 95% confidence interval were calculated in the same manner.

[1] The ICD-9 codes used for calculating this estimate were 531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, 533.6, 534.0, 534.2, 534.4, 534.6, and 578.0 – 578.9.

- Deaths per year attributable to NSAIDs in the United States
  = deaths per year from gastrointestinal bleeding (9400)
  x proportion attributable to NSAIDs (0.3662864)
  = 3443 deaths per year
- Proportion attributable to NSAIDs

$$= \frac{\text{prevalence of NSAID use (0.34) x [relative risk of GI bleed (2.7) – 1]}}{\text{prevalence of NSAID use (0.34) x [relative risk of GI bleed (2.7) – 1] + 1}}$$

  = 0.3662864

Based on the Slone Survey of American adults [Kaufman 2002], the prevalence of use for acetaminophen was estimated to be 23%. Based on consumer survey responses [Kaufman 2002], and taking into account concurrent use of two or more NSAIDs [Slone 2001], the one-week prevalence of aspirin and all other NSAID use is estimated as approximately 34%. If half of OTC acetaminophen users switched to NSAIDs, this would increase the prevalence of NSAID use to 45.5% (34% plus 11.5%). Using the formulas provided above and an Excel spreadsheet, this would result in an estimated 4100 deaths per year due to gastrointestinal bleeding from NSAID use, ie, 657 additional deaths over the current estimate of 3443. If all acetaminophen users switched to NSAIDs, it is estimated that there would be 1183 additional deaths due to gastrointestinal bleeding from NSAID use, with a total of 4626 (Figure 2-1). Thus, for each percentage point switch of acetaminophen use (eg, from 23% to 22%, or from 1% to 0%) to aspirin or other NSAIDs, an additional 42 to 64 deaths due to gastrointestinal bleeding are projected. This concern is compounded by the fact that dyspeptic symptoms do not serve to warn of impending and serious gastrointestinal complications among patients taking NSAIDs. As many as 81% of patients who had serious gastrointestinal complications had no prior gastrointestinal symptoms [Singh 1996].

2.6.2 Excess Mortality Associated with Acetaminophen Hepatotoxicity in the United States

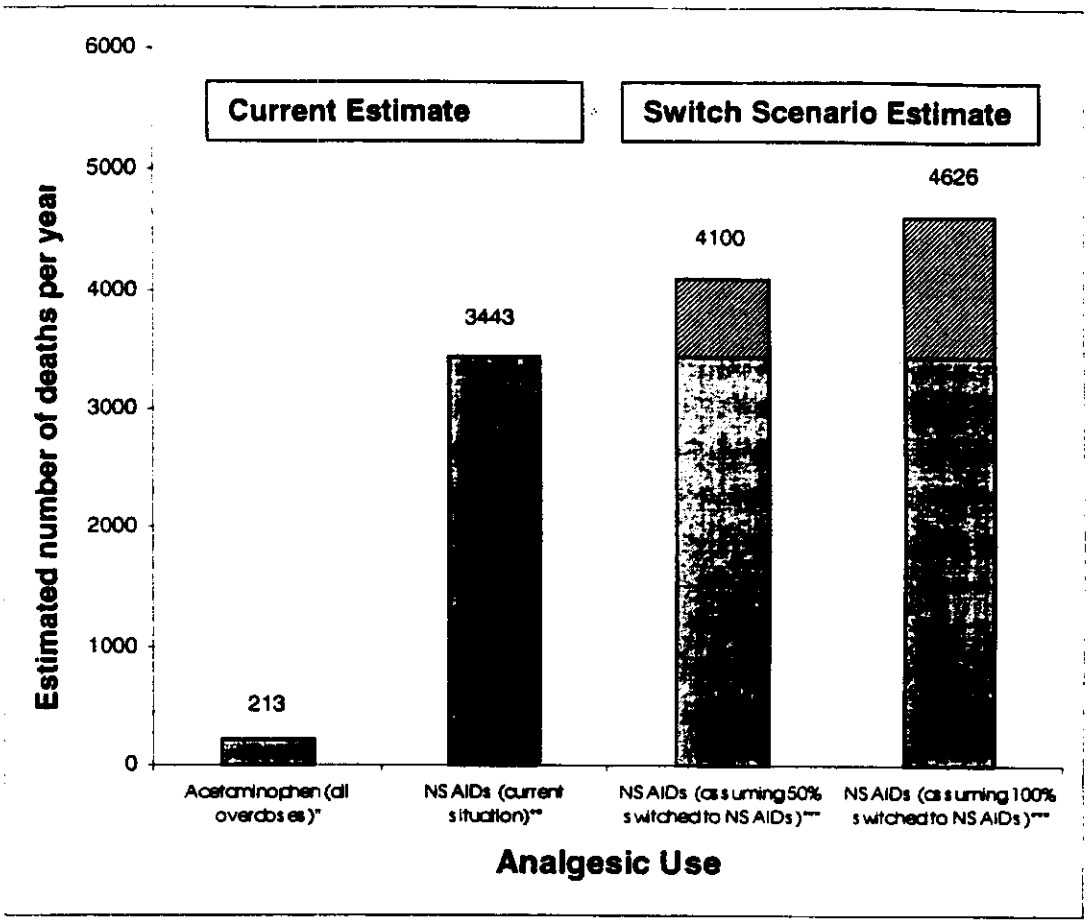
Hepatotoxicity with acute liver failure following very large overdoses is the most prominent serious adverse event associated with acetaminophen. Although there are no surveillance programs or national statistics, one personal unverified estimate is that 2000 individuals develop acute liver failure annually in the United States, and 38% of cases may be attributable to acetaminophen [Lee 2001]. A 72% survival rate has been estimated [Larson 2000]. Little has been published about these cases so it is unclear how the attribution to

acetaminophen was made or whether these estimates are accurate. However, in the absence of alternative estimates, McNeil used this information for a worst-case scenario of deaths from acetaminophen overdose: 213 per year (Figure 2-1).

2.6.3 Comparison of Excess Mortality

Figure 2-1 illustrates that the excess mortality from NSAID-related gastrointestinal bleeding at therapeutic doses far exceeds that from acute liver failure associated with acetaminophen overdoses. Even a modest shift from acetaminophen to aspirin or other NSAID use would be associated with a significant increase in the number of drug-related deaths.

Figure 2-1. Estimated Annual Excess Mortality Associated with Analgesic Use in the United States



* Personal unverified estimate of 2000 cases/year of acute liver failure, of which 38% (760) may be attributable to acetaminophen [Lee 2001]. A 72% survival rate has been estimated [Larson 2000]. 760 x 0.28 = 213.

** Estimated number of deaths per year attributable to NSAIDs in the US = deaths per year from upper GI bleeding (9400) x proportion attributable to NSAIDs (0.3662864) = 3443 deaths per year. The proportion attributable to NSAIDs was calculated as the {prevalence of NSAID use (0.34) x [relative risk of gastrointestinal bleed [Ofman 2002] (2.7) – 1]} divided by {prevalence of NSAID use (0.34) x [relative risk of GI bleed (2.7) – 1] + 1} which equals 0.3662864.

*** Prevalence of use for acetaminophen was estimated to be 23% [Kaufman 2002] and of NSAIDs to be 34% [Slone 2001]. If half of OTC acetaminophen users switched to NSAIDS, this would increase the prevalence of NSAID use to 45.5% (34% + 11.5%). This would result in an estimated 4100 deaths per year due to gastrointestinal bleeding from NSAID use, ie, 657 additional deaths over the current estimate of 3443. If all acetaminophen users switched to NSAIDs, it is estimated that there would be 1183 additional deaths due to gastrointestinal bleeding from NSAID use, with a total of 4626.

2.7 Conclusions

The risk of aspirin and other NSAID-related gastrointestinal effects occurs at recommended doses and is dose-related. At OTC recommended doses, ibuprofen appears to have the least risk of gastrointestinal toxicity when compared to other NSAIDs.

No antidote is available for aspirin or ibuprofen overdose. Acute overdose and chronic aspirin toxicity (eg, salicylism) are associated with significant morbidity and mortality (as high as 25%). In contrast, overdose with ibuprofen is relatively benign and requires supportive and symptomatic treatment only.

If acetaminophen use were to be restricted, and consequently aspirin and other OTC NSAID use increased in the United States, available data suggest that more people would die from aspirin and other NSAID-related gastrointestinal bleeding than those potentially spared from acetaminophen overdose hepatotoxicity. Even a modest shift from acetaminophen to aspirin or other NSAID use would be associated with a significant net increase in the number of drug-related deaths. This net public health impact should be taken into consideration in the formulation of any regulatory policy pertaining to OTC analgesics.

3 CONSUMER MEDICATION USE

KEY POINTS

- Acetaminophen, ibuprofen, and aspirin are the most commonly used analgesic medications in the adult population of the United States. In any given week, some 23% of adults (48.1 million people) report using acetaminophen-containing products. The estimated prevalence of aspirin use is 17% and ibuprofen use is 17%. Naproxen use is 3.5% during this same time.

- Medication use surveys provide insight regarding consumer analgesic use behaviors that may result in excessive OTC analgesic exposure.

- McNeil has implemented labeling and educational interventions aimed at focusing the attention of OTC medication users on:
  - the product ingredients
  - the proper dosing and proper use of medications
  - the importance of not taking more than the recommended dose
  - the importance of not using two products containing identical ingredients or using the same class of analgesic ingredients (eg, NSAIDs) during the same period of time
  - the importance of recognizing that all medications have risks, particularly when more than the recommended dose is taken.

3.1 Introduction

Aspirin and other OTC NSAIDs are widely used throughout the United States. A recent survey of medication use in the United States estimated that ibuprofen was taken by 17% of adults, aspirin was taken by 17% of adults, and naproxen was taken by 3.5% of adults in the preceding week [Kaufman 2002]. This section will examine recent data on consumer medication use behaviors and information regarding misuse of OTC analgesics. Based on this review, specific actions, directed at focusing the consumer on proper medication use, are discussed in Section 4, McNeil Initiatives and Recommendations.

3.2 Recent Sources of Information About Consumer Medication Use

3.2.1 Actual Consumer Medication Use

Slone Survey of Medication Use – an ongoing population-based telephone survey of medication use conducted by the Slone Epidemiology Unit (Slone) of Boston University School of Public Health [Kaufman 2002]. The survey provides recent information on use of all medications, including prescription and OTC drugs, vitamins and minerals, and herbal preparations/supplements during the 1-week period preceding a telephone interview. This survey represents a random sample of the ambulatory adult (18 years of age and older) population in the 48 continental states and the District of Columbia. As part of the interview, the participant is asked to gather the relevant bottles or packages on all medications taken during the preceding seven days.

At the request of McNeil, Slone conducted a specific analysis of utilization patterns of OTC and prescription analgesic products containing acetaminophen, aspirin, ibuprofen and naproxen based on the Survey of Medication Use. This supplemental analysis of analgesics includes a total of 6,279 participants interviewed during the time period of February 1998 through August 2001. Herein, this analysis is referred to as "Slone Survey of Analgesic Use" [Slone 2001].

The MediScope™ Household Survey – a diary-based survey of United States households demographically balanced to match US Census data provided by a market research service. Consumers are instructed to record every use of nonprescription medicine by all household members, regardless of age, for a four-week period. The data collected includes the product name, the reason for using the product, the dose amount, and the number of doses taken. Survey data is available for approximately 6700 households over a two-year time period from September 1999 through September 2001 [McNeil 2002].

3.2.2 Consumer Attitudes About Medications

McNeil Habits & Practices Survey – a telephone survey of consumer attitudes and behavior regarding use of both OTC and prescription analgesic medications conducted by a market research service. A random sample of US consumers was surveyed to identify OTC products they regularly use and their understanding of product ingredients and safety. The survey was conducted in September 2001 and sampled 410 male and female adults between the ages of 18 and 65 who had used OTC analgesics in the past six months [McNeil 2001].

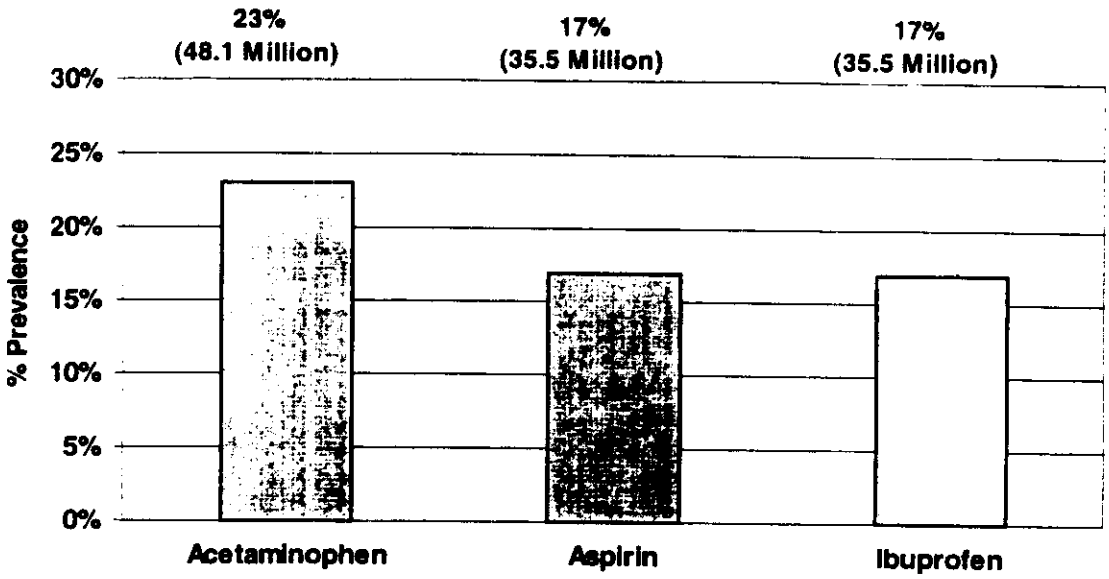
National Council on Patient Information and Education (NCPIE) Survey - a market research telephone survey of consumers and health professionals to track their opinions about the use of OTC medicines. The survey was conducted between October 25 and November 11, 2001 and consisted of two polls: one of 1011 adults 18 years of age and older and the other involving 451 pharmacists, nurses and general practice physicians. Interview questions focused on the general term of "non-prescription medicines", but did not specifically address the category of OTC pain relievers. Survey results were released to the public in January 2002 as part of the "Be Medwise" campaign [NCPIE 2002].

3.3 Patterns of Medication Use From Recent Sources

This section provides a description and perspective about patterns of use of OTC analgesics from recent sources.

According to the Slone Survey of Medication Use [Kaufman 2002], in the United States 61% of adults recall using some analgesic in the previous week. Some 23% of adults (48.1 million people) report using acetaminophen-containing products. The prevalence of aspirin use is 17% and ibuprofen use is 17%. These data are depicted in Figure 3-1. Naproxen use is 3.5% during this same time period.

Figure 3-1. One-Week Prevalence of Most Commonly Used Analgesic Products in the United States Adult Population (n= 209 million) From Slone Survey of Medication Use [Kaufman 2002]



3.3.1 MediScope™ Household Survey

The MediScope Household Survey provides additional detail about OTC medication use by adults. When the daily OTC analgesic tablet consumption by consumers is analyzed, the data in Table 3-1 show that the overwhelming majority of consumers use analgesics within the recommended OTC dose. However, a small percentage of analgesic users exceed the recommended maximum daily dose; these usage rates are 1% for acetaminophen, 6% for ibuprofen, and 13.5% for naproxen.

For aspirin, 92.4% of daily usage was 1 to 2 tablets. These data may not represent typical consumer usage of aspirin for pain relief, since approximately 52% of reportage usage was for the prevention of heart attack or stroke, situations where low-strength aspirin is recommended.

Table 3-1. Reported Distribution of Daily OTC Analgesic Tablet Consumption in an Average 4-Week Period Expressed as a Percentage of Usage Days (based on MediScope Household Survey Data from 9/99 – 9/01 [McNeil 2002])[a,b]

	Acetaminophen (8x - 500 mg tablets/day)[c,d]		Aspirin (500 mg tablet equivalent)[e]		Ibuprofen (6x – 200 mg tablets/day)[c]		Naproxen Sodium (3x – 220 mg tablets/day)[c]	
No. of Tablets	% Usage Days	Cumulative Usage %	% Usage Days	Cumulative Usage %	% Usage Days	Cumulative Usage %	% Usage Days	Cumulative Usage %
1	19.0	19.0	76.6	76.6	18.9	18.9	33.3	33.3
2	41.6	60.6	15.8	92.4	36.4	55.3	48.1	81.4
3	10.1	70.7	3.4	95.8	10.3	65.6	5.1	86.5
4	14.4	85.1	2.8	98.6	18.5	84.1	**11.5**	**98.0**
5	1.2	86.3	0.3	98.9	1.2	85.3	**0.1**	**98.1**
6	8.2	94.5	0.7	99.6	8.7	94.0	**1.3**	**99.4**
7	0.6	95.1	0.1	99.6	**0.6**	**94.6**	**0.1**	**99.5**
8	3.8	99.0	0.3	99.9	**2.4**	**97.0**	**0.3**	**99.8**
9 to 12	**0.9**	**99.9**	0.1	100.0	**2.7**	**99.7**	---	**99.8**
13 to 16	**0.1**	**99.9**	0	100.0	**0.2**	**99.0**	---	**99.8**
17 to 20	**<0.1**	**100.0**	0	100.0	**0.03**	**100.0**	**0.2**	**100.0**
% days > max. daily OTC analgesic dose	**1.0**	---	Not applicable since use not only for pain relief	--	**6.0**	---	**13.5**	---

a: Adult single-ingredient analgesic preparations (including PM product) among users 12 years of age and older.
b: Bold indicates usage days exceeding the recommended maximum daily OTC analgesic dose.
c: Total number of tablets/day to equal the recommended maximum daily OTC analgesic dose.
d: Actual mg usage (based upon intake of 325, 500, or 625 mg) standardized to 500-mg tablet.
e: Actual mg usage (based upon intake of 325 or 500 mg) standardized to 500-mg tablet.

On days that individuals used acetaminophen, 99% of usage was 4000 mg (eight tablets) of acetaminophen or less per day. Another 0.9% of acetaminophen usage was between >4000 mg and up to 6000 mg per day. Very rarely do individuals report using more than 8000 mg acetaminophen daily.

For comparison, 94% of ibuprofen daily usage was of doses of up to 1200 mg (six tablets) while 6% of daily usage exceeded 1200 mg (>6 tablets). Some 0.23% exceeded an ibuprofen dose of 2400 mg per day, while <0.03% exceeded the maximum prescription ibuprofen dose of 3200 mg per day. For consumers who use naproxen sodium, daily doses of up to 660 mg (3 tablets) represent 86.5% of naproxen sodium use, while 13.5% reported exceeding the maximum OTC daily dose, with 1.9% of the total exceeded the prescription naproxen sodium dose of 1100 mg daily. In summary, while the majority of analgesic usage is within the recommended OTC doses, a small percentage of consumers take substantially more that the recommended doses despite product labeling.

3.3.2 Slone Survey of Analgesic Use

In the Slone Survey of Analgesic Use, 79% of all aspirin users reported using a single-ingredient product [Slone 2001]. A large group (41%) of aspirin users reported a daily dose of 325 mg or less with a median duration of use of three years. This long duration is consistent with cardiovascular prophylaxis being the most frequently reported reason for aspirin use (48%). Another aspect of the aspirin usage was a pattern of concurrent use with other NSAIDs. Aspirin was used concurrently with ibuprofen, naproxen, or ibuprofen plus naproxen by a total 2.5% of subjects in the survey.

Few aspirin users reported a daily dose with their use of an OTC aspirin combination product or with use of two aspirin products concurrently. A total of 67% of OTC aspirin combination product users reported an unknown dose and 73% of those who used a single-ingredient plus a combination aspirin product reported an unknown dose (Table 3-2).

Table 3-2. Average Daily Aspirin Exposure (mg) by Type of Aspirin Product Taken (Slone Survey of Analgesic Use) [Slone 2001]

Daily Aspirin Exposure (mg)	- - - - - % of Product Category Taking Dose Within the Stated Range - - - - -		
	Use of One Product Only		Use of Two Products
	OTC single-ingredient (n= 951)[a]	OTC combination (n= 239)	OTC single-ingredient plus OTC combination (n= 11)
325 or less	50%	8%	0%
326 to 1000	17%	19%	9%
1001 to 4000[b]	4%	6%	18%
More than 4000	0.1%	0%	0%
Unknown dose	29%	67%	73%

a: Total number of users within the specified category.
b: Maximum recommended daily OTC analgesic dose indicated

In this survey, 98% of consumers who used ibuprofen reported taking only one ibuprofen product. Of this group, approximately 28% of users reported using one prescription product containing ibuprofen. Of all ibuprofen users, 34% reported an unknown dose and 66% identified a specific ibuprofen dose. Of those who reported a dose, eighty-seven percent (87%) reported a dose of no more than the maximum OTC recommended dose of 1200 mg daily. A total of 13% of ibuprofen users reported using more than the maximum recommended daily OTC dose of 1200 mg ibuprofen and 1% reported taking more than 3200 mg daily.

Some consumers do report taking more than the recommended OTC dose of ibuprofen. Table 3-3 provides a summary from the Slone Survey of Analgesic Use of the reported average daily ibuprofen exposure by type of OTC or prescription (Rx) ibuprofen product taken by consumers [Slone 2001]. In this survey, 4% of ibuprofen users taking an OTC single-ingredient ibuprofen product reported taking from more than 1200 mg to 3200 mg. For individuals taking an Rx ibuprofen product, 2% reported taking more than 3200 mg per day. In users of OTC and Rx single ingredient products, high proportions of unknown doses were reported, 31% and 42% respectively.

Table 3-3. Average Daily Ibuprofen Exposure (mg) by Type of Ibuprofen Product Taken (Slone Survey of Analgesic Use) [Slone 2001]

Daily Ibuprofen Exposure (mg)	- - - - - % of Product Category Taking Dose Within the Stated Range - - - - -			
	Use of One Product Only		Use of Two Products	Unknown Product
	OTC single-ingredient (n= 682)[a]	Rx (n= 277)	Rx + OTC single-ingredient (n= 5)	Unknown type (n= 17)
800 or less	58%	30%	0%	77%
801 to 1200[b]	7%	10%	0%	0%
1201 to 3200	4%	17%	40%	6%
More than 3200	0.1%	2%	20%	0%
Unknown dose	31%[c]	42%	40%	18%

a: Total number of users within the specified category.
b: Maximum recommended daily OTC analgesic dose.
c: One subject reported using more than 1200 mg daily (actual dose not specified).

Of consumers who reported using naproxen, 65% used an OTC product, 14% used an Rx product, 2% used two naproxen products, and 19% used an unknown naproxen product. This survey did not collect naproxen dosing [Slone 2001].

3.4 Assessment of Consumer Medication Use

Labels of OTC medications contain adequate information for safe use of a product when read and followed by a consumer. Yet reports of consumer misuse are available. McNeil is not aware of any definitive studies that examine the association between consumer medication use behaviors and increased risk, but it seems possible that some reported consumer practices, described below (in bold), may be reduced with labeling changes and dissemination of more widespread and pervasive consumer and healthcare professional education programs.

When using single-ingredient OTC analgesic products -- consumers may ingest amounts that exceed recommended dosing.

Review of recent data suggest possible reasons for this behavior:

- Pain may be so severe that extra medicine was taken for relief
- Not understanding that two products containing the same analgesic (acetaminophen or NSAID) should not be taken together in a higher than recommended single or daily dose
- Failure to read dosing instructions and warnings
- Failure to heed label warnings
- Not believing that harm could occur from taking too much medication, despite warning language
- Ingestion of alcohol or other substances that impair reasoning or judgment
- Intentional self-harm.

Even though actual medication use data indicated that excess use over the maximum daily dose is rare, in the McNeil Habits and Practices Survey 23% of consumers reported usually taking more than the OTC recommended single dose when taking the first dose of a non-prescription pain reliever. Of these respondents, the most frequent reasons why they usually take more than the recommended single dose were reported as "have multiple symptoms" (49%), "want faster relief" (19%), "have severe pain" (11%) and "told by doctor" (10%).

Similarly, among NCPIE survey respondents asked about taking more than the recommended dose of a non-prescription medicine, 33% recalled having ever taken more than the recommended dose. Sixty-eight percent (68%) of the respondents, who recalled ever taking more than the recommended dose, reported doing so because they had severe symptoms.

In the McNeil OTC Habits and Practices survey, when consumers reported using two OTC products containing the same pain reliever, they were asked why they were not concerned about this practice. Some of their responses suggest that they thought it was safe to do so: "It's safe because it is the same medicine" (27%); "I never experienced side effects" (14%), "it's safe to take together" (8%); or "OTCs are not strong enough" (5%) [McNeil 2001]. However, when asked in the survey if they think any adverse effects are possible if more

than the recommended dose is used on a regular basis, 88% said that they believed adverse side effects are possible.

These responses require cautious interpretation since they may reflect a lack of concern by consumers regarding a one-time or occasional use beyond the recommended dose.

When using single-ingredient OTC analgesic products -- consumers may take concurrently more than one OTC NSAID.

Review of recent data suggest possible reasons for this behavior:

- Not knowing the ingredients of OTC pain relievers
- Not knowing that different pain relievers contain similar ingredients
- Severe pain states causing consumers to take additional pain relievers to relieve residual pain.

Some insights about consumer knowledge of pain reliever active ingredients is found in the McNeil OTC Habits and Practices survey. When consumers were asked what active ingredient is contained in certain brands of pain reliever, the percentage of respondents who answered correctly was 68% for Bayer, 42% for Advil, 42% for Motrin, 41% for Tylenol and 10% for Aleve. In regards to concurrent use, the Slone Survey of Analgesic Use documents patterns of concurrent use of two or three different OTC NSAIDs [Slone 2001].

When using OTC combination (cough/cold) products plus single-ingredient OTC pain reliever products containing the same analgesic (acetaminophen or NSAID) -- consumers may take two (or more) OTC products for multiple symptoms, thus taking increased doses of some ingredients.

Review of recent data suggest possible reasons for this behavior:

- Not recognizing that some multi-symptom relief products contain a pain reliever
- Not recognizing the risk of taking two products containing the same active ingredient (acetaminophen or NSAID).

The McNeil Habits and Practices survey provides insight regarding these behaviors. Respondents generally were not aware that cough/cold products also contained an analgesic. Sixty-six percent (66%) of consumers knew that Tylenol Cold®, 47% knew Vick's Nyquil®, 40% knew Alka-Seltzer Plus Cold®, and 35% knew Sudafed Cold & Cough®,

respectively, contained a pain-relief ingredient (acetaminophen). For ibuprofen-containing products 69% knew that Motrin® Sinus/Headache and 62% knew that Advil® Cold & Flu contained a pain-relief ingredient. It appears that using the tradename of an analgesic (eg Tylenol or Motrin) within the name of a combination product increases consumer awareness of the analgesic component of these combination products.

3.5 Conclusions

Recent medication use surveys provide insight into consumer analgesic use behaviors that may result in excessive OTC analgesic exposure and, possibly, an increase in dose-related adverse effects or overdose.

McNeil has implemented labeling and educational interventions aimed at focusing the attention of OTC medication users on:

- the product ingredients
- the proper dosing and proper use of medications
- the importance of not taking more than the recommended dose
- the importance of not using two products containing identical ingredients or using the same class of analgesic ingredients (eg, NSAIDs) during the same period of time
- the importance of recognizing that all medications have risks, particularly when more than the recommended dose is taken.

4 MCNEIL INITIATIVES AND RECOMMENDATIONS

KEY POINTS

- Based on review of surveys regarding consumer behaviors and other available data regarding misuse of OTC analgesics, McNeil proposes that labeling and educational interventions for enhancing proper consumer behaviors should be aimed at focusing the attention of all OTC medication users on:
  - the product ingredients
  - the proper dosing and proper use of medications
  - the importance of not taking more than the recommended dose
  - the importance of not using two products containing identical ingredients or using the same class of analgesic ingredients (eg, NSAIDs) during the same period of time
  - the importance of recognizing that all medications have risks, particularly when more than the recommended dose is taken.

- Medication use surveys provide insight to formulate risk management initiatives to reduce excessive OTC analgesic exposure.

- McNeil has implemented changes to its product labeling to 1) increase the type size of active ingredient(s) on the principal display panel for all single-ingredient and combination products; and 2) present the first letter of the name of active ingredient(s) in upper case type with the remainder in lower case type. McNeil recommends these changes for all OTC analgesics.

- McNeil encourages the FDA to require labeling changes for aspirin-containing products that are consistent with those recommended for ibuprofen in the proposed amendment of the tentative final monograph (TFM) for internal analgesic, antipyretic, and antirheumatic drug products for over-the-counter (OTC) human use (67 FR 54139). McNeil recommends these changes for all OTC NSAIDs.

4.1 Introduction

Medication use surveys provide some insight regarding consumer behaviors that could result in excessive OTC analgesic exposure and, possibly, an increase in dose-related adverse effects or overdose. These behaviors affect the use of:

- Single-ingredient OTC analgesic products
- More than one OTC NSAID analgesic product concurrently
- Concurrent use of OTC single-ingredient and combination analgesic products
- Concurrent use of an aspirin- or other NSAD-containing combination prescription pain reliever and an OTC pain reliever containing aspirin or other NSAIDs

McNeil has implemented several educational initiatives to promote the safe use of OTC analgesics. In this section, we describe ongoing and proposed risk management interventions that seek to reduce the occurrence of excessive OTC analgesic exposure and potential adverse effects.

4.2 Current Labeling Initiatives

Appropriate consumer medication use requires knowledge of the safe and effective dose, as well as following the labeled contraindications, warnings about use in special circumstances, and directions when ingestion exceeds the recommended dose. Current OTC analgesic labeling explicitly warns consumers about concurrent use of multiple analgesic products, warns against taking an overdose, and provides instructions in the event of accidental overdose.

Despite these efforts, some consumers may not be aware of the specific active ingredient contained in OTC single-ingredient analgesics. In addition, some consumers may not be aware or may disregard the maximum recommended dose per administration or maximum recommended daily dose. According to results from the McNeil Consumer Habits and Practices Survey, respondents were not concerned about this practice. These responses require cautious interpretation since they may reflect a lack of concern by consumers regarding a one-time or occasional use beyond the recommended dose.

The objective of the following current McNeil initiatives and recommendations is to direct the attention and enhance awareness of consumers to key information that may reduce the occurrence of excessive analgesic exposure.

4.2.1 McNeil OTC Analgesic Product Labeling Initiatives

McNeil has revised its product labeling to further promote appropriate use of its OTC monograph acetaminophen products. McNeil has also made revisions to the labeling for its OTC Motrin® (ibuprofen) products and its St. Joseph® aspirin products.

Changes to labeling include 1) increasing the type size of active ingredient(s) on the principal display panel for all products; and 2) presenting the first letter of the name of active ingredient(s) in upper case type with the remainder in lower case type. McNeil recommends these changes for all OTC analgesics.

In light of the FDA notice of a proposed amendment of the tentative final monograph (TFM) for internal analgesic, antipyretic, and antirheumatic drug products for over-the-counter (OTC) human use (67 FR 54139), McNeil proposes that appropriate warning and precaution language also be incorporated into all ibuprofen products marketed under the NDA process as well.

McNeil encourages the FDA to require labeling changes for aspirin-containing products that are consistent with those recommended for ibuprofen in the proposed amendment of the tentative final monograph (TFM) for internal analgesic, antipyretic, and antirheumatic drug products for over-the-counter (OTC) human use (67 FR 54139). McNeil recommends these changes for all OTC NSAIDs.

4.3 Consumer and Healthcare Professional Education Initiatives

Some consumers may not be aware of the specific active ingredient contained in single-ingredient analgesics. To highlight the proper use of OTC analgesics, maximize compliance with labeling recommendations, enhance understanding of the medications consumers are using, and to caution against the use of multiple analgesics, McNeil has instituted or participated in several consumer education initiatives.

4.3.1 McNeil Education Initiatives

In March 2002, McNeil launched its "Know Your Medicine" campaign to complement another major campaign developed by the National Council on Patient Information and Education (NCPIE, described below). This initiative aims to encourage proper dosing and awareness of OTC analgesic products using three key messages:

- Read the label
- Know what's in your medicine
- Count the doses.

Consumer "touch points" for delivery of these key messages include print and radio advertising, direct mail, retail outlets, the Internet, pharmacies, and doctors' offices. Key education partners in the McNeil "Know Your Medicine" initiative include the American Academy of Family Physicians (AAFP) and the American Pharmacist Association (APhA), in addition to NCPIE. McNeil is currently identifying additional potential partnership opportunities, including other OTC manufacturers, retailers, and third party professional organizations, to further help educate consumers.

Examples of specific activities related to the "Know Your Medicine" initiative include the following:

- Distribution of over 11 million "Know Your Medicine" consumer education brochures, in English and Spanish, via retail stores, by direct mail, at pharmacy counters, and doctors' offices through 2002.
- Retailer partnerships established to develop retailer-branded brochures that incorporate the "Know Your Medicine" message (eg, CVS, Target, Walgreens, and Walmart).
- Placement of a home page promotional module on McNeil brand web sites and a link to the NCPIE Be MedWise web site.
- A direct mail and e-mail correspondence to consumers in the McNeil database following requests for additional information.
- Establishment of a professional plan for professional education.
- Use of doctors' offices to distribute additional tip cards, brochures, and sheets from patient education tear pads.
- Creation of print advertisements of pediatric dosing in English and Spanish in publications with strong parent readership.
- A campaign targeted directly to Hispanic consumers (with television, print, and radio ads).

An example of the educational content is seen in Figure 4-1 and Figure 4-2. It shows the emphasis on warning against the use of multiple products containing the same analgesic and helping consumers to identify where that might be a problem.

Figure 4-1. McNeil's Know Your Medicine Brochure (Front)

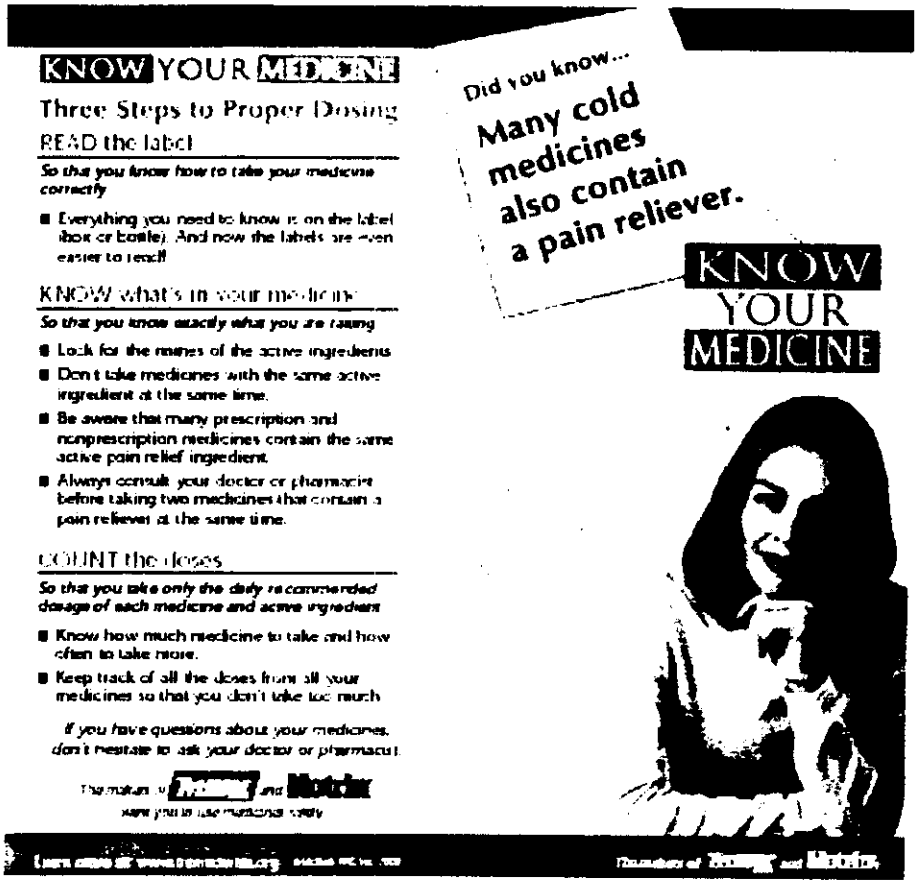
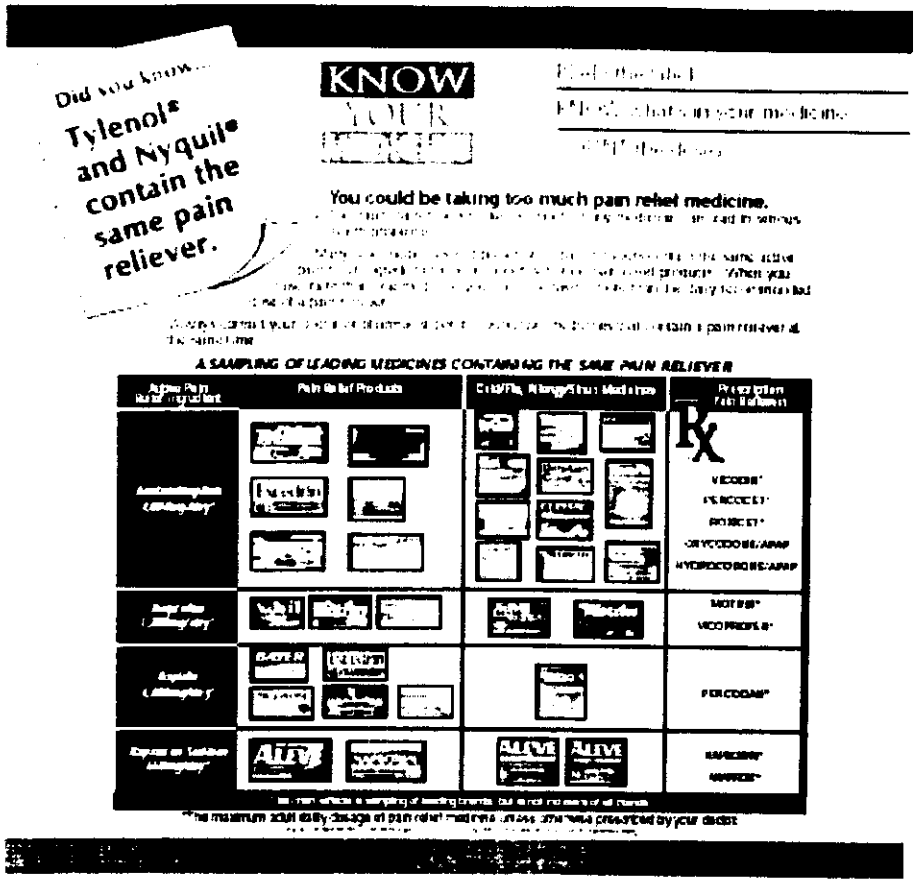


Figure 4-2. McNeil's Know Your Medicine Brochure (Back)



4.3.2 Education Initiatives - Professional and Non-Profit Organizations

NCPIE's "Be MedWise" Campaign

In January 2002, the National Council on Patient Information and Education (NCPIE) launched the nationwide "Be MedWise" program, a multi-media effort to increase public awareness of OTC product ingredients and their uses. The program was developed by NCPIE through an educational grant from McNeil. It was designed to attract support from other manufacturers as well. This effort has proven successful. On August 15, 2002, Proctor and Gamble announced its support with a $1 million educational grant toward the "Be MedWise" campaign. McNeil is optimistic that additional sponsors will participate.

The program includes television and print advertisements, as well as an Internet web site (www.bemedwise.org). Many of the materials have been developed in cooperation with the FDA. For example, NCPIE has a television advertisement aimed at avoiding the use of

more than one medication containing the same active ingredient. The ad has already reached 70% of the population and has been seen over one billion times. It features a man, who, on the advice of his wife, reads the labels of the drugs he is taking and discovers that he is taking two drugs with the same active ingredient for the same indication.

The "Be MedWise" website has been featured on CNN. Key website communication points include:

- "Know What's in Your Medicine" - designed to encourage consumers to read medication labels to understand the active ingredient(s) in the OTC product they have purchased.
- "How to Read a Drug Label" - designed to encourage consumers to read medication labels and to help them understand the safety and use information present on the label.

Phase II of the campaign, launched on May 16, 2002, features an expanded consumer-friendly website, advertisement in two issues of TIME magazine, and expanded media outreach.

Other Professional Organization Education Initiatives

McNeil initiatives include efforts to promote physicians', pharmacists', and other healthcare professionals' awareness of tools to reduce the occurrence of inappropriate OTC analgesic use. Working in cooperation with various professional organizations, McNeil has sponsored materials directed towards this objective.

For example, the American Association of Family Physicians (AAFP) has developed a monograph entitled "Appropriate Use of Common OTC Analgesics and Cough and Cold Medications" [Montauk 2002] and supporting patient education tools. This includes "Knowing What's in the Medicine You Take," a guide to using OTC pain relievers and prescription medicines. These materials were sponsored by an educational grant from McNeil. They were distributed to all 93,000 AAFP members and 30,000 high-prescribing primary care physicians.

In an effort to improve pharmacist awareness, McNeil has sponsored a National Association of Chain Drug Stores (NACDS) memo containing extensive information on the importance of proper dosing to be included in the Chain Pharmacist Practice Memo. Building on a previously established partnership with the American Pharmaceutical Association (APhA), McNeil is developing several monographs for continuing education

including "The Pharmacist's Role in Assuring OTC Medication Use," Achieving Optimal Therapeutic Outcomes with Nonprescription Analgesics," and "Health Communication in Culturally Diverse Patient Populations." These monographs will be sent to over 55,000 pharmacists in the US.

4.4 Ongoing Consumer OTC Analgesic Use Monitoring

McNeil is dedicated to evaluating the impact of its current labeling and education interventions described above on reported consumer behavior and awareness. To this end, McNeil has entered into an agreement with the Slone Epidemiology Center to expand their ongoing telephone survey of consumer behaviors regarding medications [Kaufman 2002].

Slone is adding questions to monitor changes in reported consumer behavior and to allow adjustments to OTC analgesic use-related consumer education and labeling initiatives (ie, to examine the impact of these initiatives on consumer behaviors). Data collection began in mid-June 2002. Consumers are asked about usage of any OTC analgesic product during the previous week. Respondents are asked about the dosages taken for each OTC analgesic used and sources they use to obtain information about these products. In addition, respondents are asked about their knowledge of product ingredient(s), the recommended labeled dose and knowledge of multiple-products with the same analgesic ingredient.

The periodic assessment of consumer behaviors will provide a tool to measure changes in consumer awareness and reported behaviors that arise in response to targeted messages from our consumer education programs, as well as from labeling revisions to OTC and prescription analgesic products.

4.5 Conclusions

McNeil has reviewed survey and other data that provide insights for the interventions we have implemented. These interventions are designed to target the small number of consumers who may inadvertently exceed recommended doses of OTC analgesics. Excessive doses of an OTC analgesic may be taken inadvertently because an individual does not pay attention to the product label, does not understand the product label, or is not sufficiently concerned about the potential ramifications of exceeding the recommended dose [personal communication Carr 2002]. Implemented McNeil initiatives include labeling revisions, consumer and healthcare education programs, and an ongoing consumer OTC analgesic use monitoring survey.

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Section 4 McNeil Initiatives and Recommendations

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