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McNeil
Consumer Healthcare

July 29, 2009

BY FED EX

Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research
U.S. Food and Drug Administration
White Oak Campus, Building 51-2201
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re: *Risk Management Plan for Over-the-Counter Acetaminophen Products*

Dear Dr. Woodcock:

McNeil Consumer Healthcare, Division of McNEIL-PPC-Inc. (McNeil) is requesting a meeting to establish a dialogue with the US Food and Drug Administration (FDA) on a proposed risk management program associated with the use of over-the-counter (OTC) and prescription acetaminophen-containing products. This request relates to the June 29 and 30, 2009 Advisory Committee meeting regarding potential methods of addressing the risk of acetaminophen-related overdose and liver injury.[1] As the manufacturer of numerous OTC products containing acetaminophen, aspirin and ibuprofen, McNeil is dedicated to providing consumers with safe and effective products for pain and fever relief. McNeil is also committed to working with FDA and other manufacturers to reach and implement solutions to the issues raised by the FDA and considered by the Advisory Committee. Our goal is to reduce the incidence of acetaminophen-related overdose and liver injury without creating undue burdens on consumer access to safe and effective OTC products or unintended public health consequences. This letter is intended to set

[1] *See* Joint Meeting of the Drug Safety and Risk Management Advisory Committee, Nonprescription Drugs Advisory Committee, and the Anesthetic and Life Support Drugs Advisory Committee, http://www.fda.gov/AdvisoryCommittees/Calendar/ucm143083.htm.

forth a pathway to implement effective solutions to achieve this goal. We look forward to our meeting and to working cooperatively with FDA on these matters.

As recognized by FDA's Advisory Committee, acetaminophen is extremely safe and effective when used as directed; but when more than the daily recommended dose is taken, liver injury can occur in rare instances. Although McNeil strongly believes, and the prospective data supports, that a maximum daily dose of 4000 mg under the current instructions for use is safe and effective, in order to address the risk of overdose, McNeil is proposing a comprehensive risk management program for all acetaminophen-containing products. The risk management program, which is outlined in detail below, includes education, improved surveillance and packaging and labeling changes. In addition, one of the most significant elements of the program would be an amendment to the instructions for use for OTC products containing 500 mg of acetaminophen. These changes to the instructions for use lower the maximum daily dose of acetaminophen, consistent with the Advisory Committee recommendations, to 3,000 mg, but maintain OTC access to the 1,000 mg dose for consumers who do not experience pain relief at lower doses.

As detailed below, the proposed risk management plan is the preferred permanent solution for addressing the risk of acetaminophen-related overdose and liver injury because it would address the root causes of such behaviors, but would not create undue burdens on consumer access to safe and effective products for pain and fever relief.

I. The Critical Role of Acetaminophen in the U.S. Health Care System

As FDA has acknowledged, acetaminophen is one of the most widely used and most important drugs in the United States. Acetaminophen has a long-established and well-recognized pedigree of safety and efficacy.[2] According to FDA,

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[2] *See, e.g.*, FDA, Acetaminophen Overdose and Liver Injury – Background and Options for Reducing Liver Injury (May 2009), http://www.fda.gov/downloads/AdvisoryCommittees/
(continued...)

> [a]cetaminophen is an important drug, and its effectiveness in relieving pain and fever is widely known. Unlike other commonly used drugs to reduce pain and fever (e.g., nonsteriodal antinflammatory drugs (NSAIDs), such as aspirin, ibuprofen, and naproxen), at recommended doses acetaminophen does not cause adverse effects, such as stomach discomfort and bleeding, and acetaminophen is considered safe when used according to the directions on its OTC or Rx labeling.[3]

For well over fifty years, consumers have relied on acetaminophen to reduce fever and to treat pain from headaches, muscle and back aches, minor arthritis, the common cold, toothaches, and premenstrual and menstrual cramps. In 2005 alone, consumers purchased more than 17 billion doses of OTC products containing acetaminophen.[4] The safety and efficacy of acetaminophen is well-recognized in the medical community, and acetaminophen is frequently recommended as a first-line treatment by organizations such as the American Geriatrics Society, the National Kidney Foundation, the American Heart Association, and the American College of Rheumatology.[5] Moreover, for many consumers, including those with renal disease, stomach ulcers, cardiovascular disease, and many other common conditions, acetaminophen is the most appropriate option for safe and effective OTC pain relief because of the serious and potentially fatal risks associated with taking NSAIDs.

Any risk management plan for acetaminophen-containing products must be implemented in a manner that takes into account the critically important role that acetaminophen plays in the

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CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM164897.pdf [hereinafter FDA Acetaminophen Background].

[3] 74 Fed. Reg. 18731 (Apr. 24, 2009).

[4] FDA Acetaminophen Background 1.

[5] *See, e.g.*, American Geriatrics Society, Clinical Practice Guideline (2009), http://www.americangeriatrics.org/education/pharm_management.shtml; Henrich WL, Agoda LE, Barrett B, et al., Am. J. Kidney Dis. 1996; 27:162-165; Antman EM, Bennett JS, Daugherty A, et al., Circulation 2007; 115:1634-1642; American College of Rheumatology, Arthritis Rheum 2000; 43:1905-1915.

U.S. health care system. Everyday, millions of consumers rely on the availability and effectiveness of acetaminophen products. McNeil is therefore committed to working with FDA to implement effective solutions that are cognizant of consumer need for and reliance on these products.

II. McNeil's Proposed Risk Management Program

McNeil is guided by several key principles, all of which have been expressed by FDA, Advisory Committee members, and other stakeholders.

- First, McNeil seeks to significantly reduce the incidence of acetaminophen-related overdose and liver injury. This goal can be accomplished with concerted effort by industry, FDA, and healthcare providers through a combination of various activities, including increased public education, improved surveillance, and packaging and labeling changes to prescription and OTC acetaminophen products. These efforts will address the root causes of acetaminophen overdoses and will focus primarily on reducing the number of unintentional overdose cases.[6]
- Second, steps taken to reduce the incidence of overdose and liver injury should not limit consumer access to important OTC medicines. Any action by FDA and industry should not create unnecessary cost or time burdens for consumers, caretakers, or healthcare providers in accessing safe and effective pain relief products. McNeil believes that such burdens could lead to a situation in which many consumers' pain relief needs are not being addressed, which is certainly not the intended outcome.
- Third, any efforts at reducing acetaminophen-related overdose and liver injury should not have the unintended consequence of causing consumers to switch to other OTC medications that may be less appropriate or less safe. If a safe and effective dose of acetaminophen is not available to consumers in the OTC market, they may switch to ibuprofen or other NSAIDs, the primary OTC alternative to acetaminophen, for their pain relief needs. As FDA has recognized, NSAIDs are associated with serious safety risks, including but not limited to gastrointestinal adverse events.[7] For most consumers, switching from acetaminophen to NSAIDs would not result in a net gain in safety. In fact, causing consumers to switch from acetaminophen to NSAIDs would likely result in

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[6] Acetaminophen Hepatotoxicity Working Group, Recommendations for FDA Interventions to Decrease the Occurrence of Acetaminophen Hepatotoxicity 4 (Feb. 2008) [hereinafter Acetaminophen Working Group Report].

[7] *See, e.g.*, 74 Fed. Reg. 18731 (Apr. 24, 2009).

increased morbidity and mortality from gastrointestinal bleeding and renal failure. This would be the case even when one assumes only a minimal shift to NSAID use. Moreover, many consumers have been directed by their healthcare provider not to take NSAIDs for various reasons. These consumers need other options for effective OTC pain relief products, and acetaminophen often represents the safest and most effective option.

- Fourth, McNeil is cognizant that consumers face many different messages about directions, warnings, and other issues for various products in the OTC market. In order to reduce consumer confusion, any action should be supported by extensive consumer outreach and education. Similarly, any new instructions for use for OTC acetaminophen products should be consistent with instructions that consumers are already familiar with, thereby increasing the likelihood that they will be able to understand and follow the new instructions.
- Fifth, McNeil seeks to take swift action to address these issues. This proposed risk management program allows for changes to be executed in a timely manner.
- Finally, McNeil believes that an effective solution requires a commitment not just on its part, but by the entire industry. An industry-wide plan is critical to create consistency across acetaminophen products, avoid consumer confusion, and reinforce the importance of following dosing directions in order to reduce the risk of overdose and liver injury.

Keeping in mind these important principles, McNeil is proposing a comprehensive risk management program for OTC and prescription acetaminophen-containing products. This risk management program would have numerous elements, including public outreach and education, surveillance activities, and packaging and labeling changes. This program would embrace nearly all of the actions discussed and recommended by the Advisory Committee and would include the following elements described below.

A. Reducing Liver Injuries in Infants and Children

In order to reduce the incidence of acetaminophen-related liver injury in infants and children, the risk management program would target both accidental unsupervised ingestions of acetaminophen and unintentional medication errors.

- Limit OTC pediatric acetaminophen liquid products to a single concentration of 160 mg acetaminophen per 5 milliliters

- Include in-pack validated dosing device with flow restrictor in all pediatric liquid OTC acetaminophen products[8]
- Establish a requirement in "Directions" labeling to use in-pack measuring device
- Add dosing directions on OTC label of acetaminophen infant's product for 6 months to <2 months of age; highlight new dosing directions on package
- Communicate new "Under 2 dosing directions" to consumers and healthcare professionals
- Standardize dosing abbreviations and volumetric measures in dosing directions for all OTC products for pain and fever relief
- Evaluate and test enhanced messages ("Don't use adult medicines in children" and "Don't give more than the recommended dose" and "Keep medicines out of the reach of children")

B. Reducing Liver Injuries in Adults

In order to reduce the incidence of acetaminophen-related overdose and liver injury in adults, the risk management program would focus on unintentional medication errors but would also address intentional ingestions of acetaminophen.

- McNeil would make significant amendments to the instructions for use for 500 mg acetaminophen-containing OTC products, which will reduce the daily maximum dose and allow consumers to titrate up from the lowest effective dose, if necessary. The content of these amended instructions, along with the justification for this proposed course of action, is addressed in detail in the next section of this letter.
- Work with FDA and other stakeholders to design and implement an enhanced surveillance system to augment existing data surveillance tools in order to better understand clinical and behavioral characteristics of individuals with acetaminophen-related overdose and liver injury

[8] McNeil already has an in-pack validated dosing device in all of its pediatric liquid OTC acetaminophen-containing products.

- Develop a research agenda in collaboration with external stakeholders to generate additional data with respect to putative at-risk populations and their potential to develop liver injury when taking recommended doses of OTC acetaminophen products
- Assess the potential for packaging to decrease the magnitude of exposure in the event of impulsive intentional overdose without causing unintended consequences
- Communicate appropriate messaging around label warning regarding acetaminophen overdose and liver injury as well as the need for quick medical attention even if no signs or symptoms
- Determine target users who take more than recommended dose by using surveys and/or other appropriate methodologies
- Develop and test optimal methods to communicate acetaminophen as an ingredient in OTC and prescription products and implement appropriate solutions
- Reinforce and enhance messages ("Don't take more than the recommended dose") to consumers and healthcare professionals
- Communicate appropriate messaging around liver damage warning

All of these elements would help to address the causes of acetaminophen overdose in children and adults, which include not following dosing directions, taking multiple acetaminophen-containing medicines at once, intentional overdoses, accidental pediatric ingestions, not properly using infants' formulations, and administering adult medicines to children. The surveillance elements of the risk management plan would ensure that FDA and industry have the necessary data and other information to determine if any changes are needed to the risk management elements. Unlike other proposals, these risk management elements would reduce the incidence of liver injury, but would not unduly burden consumer access or drive consumers to NSAIDs and thereby significantly increase the number of adverse events associated with OTC pain relief products.

III. McNeil's Proposed Changes to the Instructions for Use for Adult 500 mg OTC Acetaminophen Products

As part of the comprehensive risk management program described above, McNeil is proposing to significantly amend the current instructions for use for adult single-ingredient and

combination OTC products containing 500 mg of acetaminophen. The new instructions would state:

- do not take more than directed
- the smallest effective dose should be used
- take 1 tablet every 4 to 6 hours while symptoms persist
- if pain or fever does not respond to 1 tablet, 2 tablets may be used
- do not exceed 6 tablets in 24 hours, unless directed by a doctor

These changes would in effect lower the maximum total daily adult dose, as recommended by the Advisory Committee, to 3,000 mg and would direct consumers to begin with one 500 mg tablet, rather than beginning with the full 1,000 mg dose. These changes, however, would maintain OTC access to the 1,000 mg dose for those consumers who do not experience pain relief at lower doses and for those consumers who, for various reasons, cannot take other types of OTC pain relievers. Additionally, physicians could still recommend a 4,000 mg maximum daily dose as professional dosing for patients in need of 24-hour relief for more chronic pain conditions. McNeil believes that the proposed instructions for use, as a critical part of the comprehensive risk management program, are the best strategy to achieve all of the shared principles discussed above.

A. The Proposed Changes Would Reduce the Incidence of Liver Injury

Although McNeil strongly believes, and the data supports, that the 4,000 mg maximum daily dose under the current instructions for use is safe and effective, the proposed change would introduce an additional margin of safety by reducing the OTC maximum daily dose of acetaminophen by twenty-five percent. Current data show that the risk of acetaminophen-related liver injury for the general population does not occur until well above the current 4,000 mg maximum daily dose. Estimates at the lower end range from 5 to 7.5 grams per day.[9]

[9] FDA Acetaminophen Background 3, 9.

Decreasing the OTC maximum dose to 3,000 mg thus would allow for greater room for error for those consumers who ingest more than the daily recommended dose. Even under conservative estimates of the doses needed to cause liver injury, a consumer would need to ingest nearly twice the maximum daily dose to be at risk. As FDA has stated, "the currently recommended dose of 4 grams per day is considered safe for most people," so the goal of reducing the maximum daily dose is not to adjust the safe dose when the products are used as directed but to "reduce unintentional overdose associated with misuse and duplicate dosing."[10] A maximum daily dose of 3,000 mg would be safe for the general population and is even lower than the maximum daily dose of 3,250 mg recommended by the FDA Acetaminophen Hepatotoxicity Group in its 2008 report.[11]

FDA's own data demonstrate that liver injury is caused by consumers taking more than the daily recommended dose of acetaminophen, rather than taking more than the single recommended dose.[12] Any dosing changes should therefore address the maximum daily dose.

By directing consumers to start with one tablet and to take the lowest effective dose, these instructions for use also would reduce consumers' overall acetaminophen exposure. While McNeil's data show that many consumers already take just one 500 mg tablet at a time or switch between taking one or two 500 mg tablets, these directions would clarify that all consumers should begin by taking one 500 mg tab Taking the lowest effective dose is consistent with the tenets of good medicine. The new directions for use would give consumers an opportunity to determine whether the lower dose is effective for them, thereby reducing overall acetaminophen exposure for those consumers who receive effective relief at 500 mg.

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[10] *Id.* at 9.

[11] Acetaminophen Working Group Report 10.

[12] *See, e.g.*, 71 Fed. Reg. 77314, 77335-36 (Dec. 26, 2006).

B. The Proposed Changes Would Ensure Continued Consumer OTC Access to Effective Pain Relief Products

Data consistently demonstrate that for many consumers, the 1,000 mg acetaminophen dose provides effective pain relief that cannot be achieved at lower doses. It is therefore critical to maintain consumer access to the OTC 1,000 mg dose. Although the Advisory Committee voted in favor of eliminating the 1,000 mg dose from the OTC market, such a change would adversely affect a significant population of consumers. If the 1,000 mg dose were switched to prescription status, those consumers who need such a dose for pain relief may not receive adequate analgesia or would face increased cost, time, and other hurdles in obtaining pain relief with acetaminophen. Such a change would be particularly burdensome for poor, elderly, or disabled consumers or consumers who live in rural environments where access to a physician and a pharmacy may be limited.

The burden caused by eliminating the 500 mg formulation from the OTC market would be especially problematic given that this action would not significantly address the primary root cause of acetaminophen-related overdose and liver injury. As discussed above, FDA's own data suggest that liver injury is primarily caused by taking more than the recommended daily dose, not taking more than the recommended single dose. Unlike other proposals, McNeil's proposed instructions of use would focus on addressing this root cause, but would do so without creating barriers to consumer access to safe and effective OTC products.

Moreover, FDA and other stakeholders have recognized that the 1,000 mg maximum single dose is safe and effective when used as directed.[13] Indeed, the 1,000 mg acetaminophen dose has been available in the OTC market for over 35 years.[14] In 1973, FDA approved a 500 mg acetaminophen capsule for OTC use. Two double-blind, controlled studies showed that a

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[13] *See, e.g.*, 74 Fed. Reg. 18731 (Apr. 24, 2009); *see also* Acetaminophen Working Group Report 4 ("The ability of acetaminophen to cause liver toxicity when it is improperly used is not a reason to discourage its proper use.").

[14] *See* 71 Fed. Reg. 77314, 77335 (Dec. 26, 2006).

single dose of two 500 mg capsules was "significantly more effective" than the previously approved 650 mg single dose. The studies also showed that the safety profile of the 1,000 mg dose was similar to the 650 mg dose.[15] As part of the OTC Drug Review, the Internal Analgesic, Antipyretic, and Antirheumatic Panel recommended in 1977 that acetaminophen be generally recognized as safe and effective and recommended a maximum single dose of 1,000 mg. The Panel's recommendation of 1,000 mg as the maximum single dose was adopted in the proposed monograph published in 1977 and in the 1988 tentative final monograph as well.

Despite this long-standing history of safety and efficacy, McNeil's proposal would reduce the number of consumers actually taking the 1,000 mg dose by instructing consumers to take the lowest effective dose and to start with one 500 mg tablet. In effect, those consumers who need the 1,000 mg dose (as determined after having tried the 500 mg dose) would have access to their needed dose, and consumers who do not need the 1,000 mg dose would be instructed to take a lower dose. McNeil's proposal therefore properly balances the need to reduce the incidence of overdose and liver injury with the need to maintain consumer OTC access to safe and effective pain relief products.

C. Unlike Other Proposed Solutions, Amending the Instructions for Use Would Limit the Unintended Consequences of Consumers Switching to Other OTC Products

Data demonstrate that a 650 mg acetaminophen dose is less effective than 1000 mg acetaminophen and the maximum OTC ibuprofen dose. Additionally, 650 mg acetaminophen provides a shorter duration of pain relief compared to the currently available maximum ibuprofen OTC dose. If FDA were to limit the maximum single OTC acetaminophen dose to 650 mg as recommended by the Committee, those consumers who do not experience sufficient pain relief at this lower dose may switch to NSAIDs. FDA and other stakeholders have stated

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[15] *Id.*

that they wish to avoid such an unintended consequence because of the unique and potentially fatal risks associated with NSAIDs, including gastrointestinal risks and cardiovascular toxicity.[16]

In considering the risk of consumer shift to NSAIDs, current acetaminophen usage must be taken into account. 500 mg OTC acetaminophen tablets represent ninety-two percent of U.S. sales of single ingredient acetaminophen products.[17] Removing these products from the shelves is likely to shift a significant number of consumers to NSAIDs, which may have greater safety consequences than any associated with maintaining the 500 mg acetaminophen formulation. Published research suggests that even at OTC doses, NSAIDs, including ibuprofen, have an increased relative risk for gastrointestinal bleeding.[18] Indeed, the FDA Acetaminophen Working Group stated that "a major switch to NSAIDs for treatment of chronic pain in people now using acetaminophen would not represent a safety gain."[19] In fact, a consumer shift to NSAIDs may result in a safety loss, including increased serious adverse events and deaths. This potential increase in serious adverse events and death stems from the fact that the population risks from

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[16] *See, e.g.*, Acetaminophen Working Group Report 9 ("Chronic use of NSAIDs is also associated with significant morbidity and mortality. NSAID gastrointestinal risk is substantial, with deaths and hospitalization estimated in one publication as 3200 and 32,000 per year respectively. Possible cardiovascular toxicity with chronic NSAID use has been a major discussion recently."); *see also id.* at 4 (stating that the goal of any measures should be "to reduce acetaminophen-related hepatotoxicity, not to decrease appropriate acetaminophen use or to drive people to use NSAIDs instead").

[17] FDA Acetaminophen Background 9.

[18] Mellemkjaer L, Blot WJ, Sorenson HT, et al. Upper gastrointestinal bleeding among users of NSAIDs: a population-based cohort study in Denmark. Br J Clin Pharmacol 2002; 53:173-181.

Garcia Rodriguez LA, Jick H. Risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs. Lancet 1994;343:769-772.

Garcia Rodriguez LA, Barreales Tolosa L. Risk of upper gastrointestinal complications among users of traditional NSAIDs and COXIBs in the general population. Gastroenterology 2007;132:498-506.

[19] Acetaminophen Working Group Report 19.

acute gastrointestinal bleeding and acute renal failure caused by NSAIDs are far greater by orders of magnitude than the risk of acute liver failure from all causes.

Not only would some consumers switch to NSAIDs, other consumers, who for various reasons cannot take NSAIDs and do not obtain pain relief at 650 mg acetaminophen dose, would have no access to the most appropriate OTC pain relief medication. For example, acetaminophen is the preferred analgesic for consumers with renal disease, stomach ulcers, cardiovascular disease, and many other common conditions. In short, some consumers have no option for safe, effective, and convenient pain relief other than a 1,000 mg acetaminophen dose in an OTC product. FDA has recognized the importance of keeping an effective acetaminophen product on the market, stating that "[c]ompared to alternative pain medications, principally narcotics and NSAIDs, it is relatively safe when used correctly and provides an important option compared to other pain medications."[20]

Unlike the Committee's recommendation to eliminate the 1,000 mg OTC dose, these instructions for use changes would limit the unintended consequences of consumers switching to NSAIDs while still reducing the likelihood of acetaminophen-related overdose and liver injury. Keeping the 500 mg formulation on the market would give consumers an effective, non-NSAID pain relief option, but changing the instructions for use would reduce consumers' overall exposure to acetaminophen.

D. **Consumers Would Be Able to Understand and Follow the Proposed Instructions for Use**

McNeil's proposed labeling is similar to the OTC instructions for use for ibuprofen, which instruct consumers to use the lowest effective dose, to begin with one tablet, to use two tablets if pain or fever do not respond, and not to exceed a certain number of tablets in 24 hours. These directions have been used

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[20] *Id.* at 4.

since ibuprofen was first approved for OTC use in 1984,[21] so consumers are accustomed to these directions and would be able to understand and follow them. Consumers face countless different products, formulations, and instructions in the OTC marketplace, and using directions that consumers already recognize would help to reduce any consumer confusion about proper dosing or other issues. Moreover, switching the dosing directions for 500 mg acetaminophen products to a version similar to those for ibuprofen would increase consistency across OTC internal analgesic products and would reinforce the idea that all OTC pain relievers have risks and that the lowest effective dose for all products should be used.

In order to inform current and future acetaminophen users of the changes in dosing instructions for the 500 mg product, McNeil, working with industry, would design and implement a comprehensive, multi-faceted, multi-year educational effort. Such an effort would be aimed at consumers, caretakers, and healthcare professionals. The educational activities would serve not only to direct consumers' attention to the new instructions, but also to increase consumer awareness that improperly taking acetaminophen can cause liver injury and that consumers should read and follow the label for all OTC products. These efforts also would reduce consumer confusion resulting from the various proposed changes to OTC acetaminophen products.

E. **McNeil Could Quickly Implement the Instructions for Use Amendments**

If FDA were to approve of the proposed risk management plan, including the instructions for use amendments, McNeil could implement these changes in a relatively short period of time, and we could immediately implement our educational efforts informing consumers of the impending changes to the instructions for use. Other proposals could take significantly longer to

[21] *See* Physicians' Desk Reference 1985 (Nuprin, Advil).

implement. For example, removing the 500 mg formulation from the OTC market would require FDA to amend the tentative final internal analgesic monograph. Such action would require notice and comment rulemaking, which would take at least a year to complete, as well as a necessary implementation period. The risk management plan, and the instructions for use amendments, would not require such a significant amount of time to implement and would therefore more immediately address the risk of liver injury without engendering unintended consequences.

IV. McNeil is Committed to Working with FDA to Implement All of These Efforts

The combination of the proposed instructions for use amendments and the other risk management elements would significantly reduce the incidence of acetaminophen-related liver injury. Striking the proper balance between the risk of such injuries and maintaining consumer OTC access to effective pain relief products without creating unintended consequences is a critical task, and we appreciate the ongoing opportunity to communicate with FDA regarding this issue.

We are interested in meeting with the FDA as soon as possible. We will make every effort to accommodate the date and time proposed by the FDA. In the meantime, please do not hesitate to contact me should you have any questions about our proposal.

Sincerely,

Lynn A. Pawelski
Vice President, Regulatory Affairs

cc: Dr. Gerald Dal Pan
Dr. Charles Ganley
Dr. Sharon Hertz
Dr. Sandra Kweder