

**EXECUTIVE SUMMARY**

**MCNEIL CONSUMER HEALTHCARE'S RESPONSE  
TO FDA'S PROPOSED RULE [71 FR 77314-52]**

The Food and Drug Administration (FDA), an Agency of the Department of Health and Human Services, has published in the Federal Register Vol. 71 No. 247, on December 26, 2006, a Proposed Amendment of the Tentative Final Monograph for Internal Analgesic, Antipyretic, and Antirheumatic (IAAA) Drug Products for Over-the-Counter (OTC) Human Use. This document specifically addresses proposals to change required warnings and other labeling. McNeil Consumer Healthcare (McNeil) of Fort Washington, Pennsylvania, submits herein a detailed response to the Agency's proposed amendment. McNeil also responds to FDA's invitation to comment on a number of additional issues for consideration.

The document is organized as follows:

- Item 1: McNeil's Response to FDA's Proposed Labeling for OTC Acetaminophen Products
- Item 2: McNeil's Response to FDA's Request for Comments and Data
- Item 3: McNeil's Response to FDA's Proposed Labeling for OTC Non-Steroidal Anti-Inflammatory Drug (NSAID) Products

McNeil, a major manufacturer of OTC IAAA drug products, markets a comprehensive line of Tylenol® (acetaminophen) brand single-ingredient and combination-ingredient products for adults and children, as well as acetaminophen-containing products under the Sudafed® and Benadryl® brand names for adults. McNeil also markets Motrin® (ibuprofen) products for use by adults and children, as well as St. Joseph® aspirin (81 mg) for use by adults only. As a major manufacturer of OTC IAAA drug products, McNeil is committed to encouraging scientifically appropriate and adequate labeling that includes consistent, clear, and appropriate language for consumer use.

In this submission, McNeil provides comments on FDA's proposed warnings and other labeling for acetaminophen-containing products and NSAIDs, FDA's scientific conclusions regarding the characteristics and consequences of unintentional acetaminophen overdose, and FDA's requests for comments on other related scientific matters.

## **1 EXECUTIVE SUMMARY: ITEM 1: MCNEIL'S RESPONSE TO FDA'S PROPOSED LABELING FOR OTC ACETAMINOPHEN PRODUCTS**

Item 1 of McNeil's submission responds to FDA's proposed labeling changes for OTC acetaminophen products. McNeil agrees with FDA about the important role of labeling and education to help to minimize misuse of OTC analgesic products. Some specific modifications to FDA's proposals are discussed herein.

McNeil is committed to encouraging scientifically appropriate and adequate labeling for OTC analgesic drugs, which includes consistent and clear language for consumer use, and educating consumers and healthcare professionals on the appropriate use of OTC analgesic products.

Prior to and since FDA's 2002 Nonprescription Drugs Advisory Committee (NDAC) meeting, McNeil voluntarily implemented statements on the labeling of its pediatric and adult Tylenol acetaminophen products that are similar to those now proposed in FDA's proposed rule. McNeil voluntarily:

- Added "Do not use with other products containing acetaminophen" in the warnings section
- Added "Taking more than the recommended dose (overdose) may cause serious health consequences" in the overdose warning; subsequently changed "serious health consequences" to "liver damage"
- Increased prominence of "acetaminophen" on the front of the OTC carton
- Added "Do not take more than directed (see overdose warning)" in the directions section
- Added "Do not use this adult product in children under 12 years of age; this will provide more than the recommended dose (overdose) and may cause liver damage" in the directions section

### **1.1 General Comments**

McNeil concurs with FDA's statements [71 FR 77314 at 77315] that OTC acetaminophen-containing products:

- are safe and effective when labeled appropriately and used as directed
- benefit tens of millions of consumers every year

- should continue to be accessible to consumers in the OTC setting
- have long been effective for the intermittent treatment of minor aches and pains and fever

FDA states in its proposed rule, “at their (ie, OTC acetaminophen-containing products) recommended doses, these products are only rarely associated with serious adverse events relative to the number of consumers who use these products.” [71 FR 77314 at 77315]. Elsewhere in FDA’s proposed rule, FDA specifies liver injury as the “serious side effects” that can occur with acetaminophen.

FDA’s statements inaccurately reflect the currently available science, which shows hepatic injury can occur following substantial acetaminophen overdose, but does not show a risk of hepatic injury with the maximum labeled daily dose of acetaminophen, regardless of population. While there exists retrospective case reports of serious hepatic events reported to involve acetaminophen-containing products, the information reported from these cases are inherently of limited value and provide no reliable evidence of toxicity at recommended OTC doses of acetaminophen. FDA’s tentative conclusions provide clarification about acetaminophen overdose and toxicity by stating that, “when taken in excess amounts, acetaminophen can cause liver injury.” FDA notes the rarity of such events by stating that, “when compared to the extensive use of OTC acetaminophen drug products, the incidence of injury appears relatively low.” [71 FR 77314 at 77331] McNeil agrees that the available science supports these two FDA concluding statements. However McNeil disagrees with any suggestions that the current science supports any conclusion regarding injury at the maximum-labeled daily dose.

## **1.2 McNeil’s Response to FDA’s Proposed Labeling for OTC Acetaminophen Products**

### **1.2.1 Alcohol Warning**

Based on currently available science, including results from new prospective, double-blind, randomized, placebo-controlled, clinical studies, an alcohol warning for OTC acetaminophen products is not necessary. Both FDA’s current alcohol warning and FDA’s proposed alcohol warning (as part of a proposed new liver warning) specifically and inappropriately place an alcohol warning in the context of recommended use and dosing of acetaminophen. Neither of these warnings is consistent with currently available science.

The scientific evidence, including results from new prospective, double-blind, placebo-controlled, randomized, clinical studies, supports that individuals with a history of alcohol use can safely take maximum-labeled daily doses of acetaminophen, and that the only risk of hepatotoxicity is when taking more than the recommended dose (overdose). Therefore, it is not necessary or appropriate to specifically call out a subpopulation that uses or abuses alcohol, since an overdose risk applies to the entire general population and not just to this subset population.

Despite this, if FDA moves forward with some type of alcohol warning on OTC acetaminophen-containing products, it must be modified to precisely reflect the available scientific evidence of a potential risk from overdose:

McNeil Proposal –Modification of FDA’s Current Alcohol Warning

“Alcohol Warning: If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take acetaminophen or other pain relievers/fever reducers. Taking more than the recommended dose (overdose) of acetaminophen may cause liver damage.”

**1.2.2 Liver Warning**

McNeil agrees that FDA’s proposal to add a liver warning is an acceptable revision, but disagrees with FDA’s proposed wording, which inappropriately implies a risk with taking the maximum labeled daily dose of acetaminophen and incorporates an alcohol warning as part of the liver warning in an attempt to save label space. McNeil’s proposed language for a liver warning explicitly informs consumers that the risk behavior is from taking more than the recommended dose (overdose). Because the only risk behavior leading to liver damage is from taking more than the recommended dose of acetaminophen, it is not necessary to call out those individuals who use or abuse alcohol in this warning, since an overdose risk applies to everyone.

McNeil Proposal – Liver Warning (Products Labeled for Adults)

“**Liver warning:** This product contains acetaminophen. Liver damage may occur if you take more than the recommended dose (overdose).

Do not:

- Take more than 8 caplets in 24 hours
- Use with other drugs containing acetaminophen”

### **1.2.3 Concomitant Use Warning**

McNeil agrees in principle with FDA's proposal to help consumers avoid concomitant use of more than one acetaminophen-containing product, but disagrees with FDA's proposed wording, because it does not provide enough information about what question to ask the doctor or pharmacist. In order to more clearly identify for the consumer what question they should ask their doctor or pharmacist, McNeil recommends alternate language be used in place of the FDA's proposed wording.

#### McNeil's Proposal - Concomitant Use Warning

"Do not use with any other drug containing acetaminophen (prescription or non-prescription). If you are not sure whether a drug contains acetaminophen, ask a doctor or pharmacist."

### **1.2.4 Preexisting Liver Disease Warning**

McNeil disagrees with FDA's tentative conclusion that preexisting liver disease is a risk factor for developing hepatotoxicity with therapeutic doses of acetaminophen. Based on available clinical science, stable chronic liver disease, in the presence or absence of alcohol, does not result in hepatotoxicity at maximum labeled daily doses of acetaminophen. Based on the body of scientific evidence and new clinical data, the addition of FDA's proposed labeling text: "Ask a doctor before use if you have liver disease" is not warranted.

Additionally, OTC acetaminophen-containing products can be used safely in adults with preexisting liver disease and are preferred to aspirin and other NSAIDs in this subpopulation because of the increased renal sensitivity and gastrointestinal bleeding risk in this subset population.

### **1.2.5 Additional Opportunities to Minimize Unintentional Overdose**

FDA has identified the following as reasons for unintentional overdose in adults, "the failure of prescription container labels to list acetaminophen as an ingredient" and "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." McNeil encourages FDA, Pharmacy and Medical Associations and other interested stakeholders to work to improve container labels of prescription acetaminophen-combination products, to increase consumer understanding that prescription

acetaminophen-combination products contain the active ingredient “acetaminophen”, and to improve the education of healthcare professionals on these matters.

Currently OTC pediatric acetaminophen products do not contain dosing information for children < 2 years old, McNeil strongly requests that FDA issue a formal response to McNeil’s Citizen Petition of February 1999 (FDA docket 77N-0094) and provide OTC acetaminophen dosing directions for children under two years of age on the OTC acetaminophen consumer package.

### **1.3 Introduction to McNeil’s Comments and Discussion of New Scientific Data**

In an effort to properly respond to FDA’s proposed rule, McNeil acquired, evaluated, and summarized new data from clinical safety and metabolism studies, newer published research since FDA’s data review cut-off date of 2003, important data that FDA omitted in its review, and new analyses of epidemiological data. McNeil provides new and updated scientific evidence regarding the threshold for acetaminophen overdose toxicity, and a critique and further analysis of databases cited in the proposed rule. McNeil also provides the following:

- a review of acetaminophen metabolism and its implication for the safety of acetaminophen in individuals who have preexisting liver disease
- new data from an acetaminophen metabolism study in adults with moderate hepatic impairment very recently completed by McNeil
- a review of the safety of maximum labeled daily doses of acetaminophen in individuals who consume alcohol, including new clinical safety data from three additional prospective, placebo-controlled, studies of acetaminophen use at maximum therapeutic doses over 2-to-5 days, in chronic alcohol abusers.

#### **1.3.1 McNeil’s Position on Threshold of Toxicity for Acetaminophen**

McNeil does not agree with FDA’s assessment of the toxicity threshold of acetaminophen [71 FR 77314 at 77336]. Data do not support the assertion that repeated, suprathreshold ingestions of less than 10 g/day present a risk for hepatic injury. Instead, prospective data indicate that the threshold for toxicity is a repeated suprathreshold ingestion of acetaminophen of at least 10 g/day for at least two to three days.

- When comparing toxicity from acute overdoses and toxicity from repeated suprathreshold overdoses, prospective pharmacokinetic and metabolism studies

indicate that the hepatotoxic potential would be less if the overdose is divided over an entire day (repeated suprathapeutic overdose) as opposed to when the overdose is taken all at once (acute overdose).

- The maximum labeled daily dose for acetaminophen is 4 g/day. Ingestion of more than 4 g in a 24-hour period is defined as an overdose. Ingestion of more than 4 g in an 8-hour period is defined as an acute overdose. Ingestion of more than 4 g/day in divided doses is defined as repeated suprathapeutic ingestion. However, taking more than the maximum-labeled daily dose (overdose) in any one of these scenarios does not define the threshold for toxicity.
- New data from a pharmacokinetic/metabolism study demonstrate the safety of repeated suprathapeutic doses of 6 or 8 g/day in healthy volunteers, where doses up to 8 g/day for three days were given without evidence of hepatotoxicity as measured by aspartate aminotransferase (AST) and alanine aminotransferase (ALT). In fact, in this study, repeat dosing was shown to increase the liver's ability to form nontoxic glucuronide metabolites, while not increasing the production of thiol metabolites (ie, not increasing the amount of the toxic intermediate).
- A prospective, observational case series of repeated suprathapeutic overdoses indicate that the threshold for toxicity is a repeated suprathapeutic ingestion of at least 10 g/day for at least two to three days. In this study, subjects who report having taken repeated suprathapeutic ingestion showed:
  - no evidence of an elevation in aspartate aminotransferase (AST < 50), when the average reported dose was 10.6 g/day (CI: 9.4 to 11.7) taken for a median duration of 37 hours;
  - evidence of some level of AST elevation (AST ≥ 50 < 1000 IU/L), when the average reported dose was 11.7 g/day (CI: 9.6 to 13.8) taken for a median duration of 48 hours; and
  - evidence of hepatotoxicity (AST > 1000 IU/L), when the average reported dose was 12.6 g/day (CI: 10.3 to 14.9) taken for a median duration of 72 hours.

### **1.3.2 McNeil's Critique and Analysis of Databases Cited in the Proposed Rule**

McNeil disagrees with some of FDA's conclusions drawn from assessment of the case series and databases cited in the proposed rule. It is inappropriate for FDA to use such

case series and databases to support proposed labeling recommendations that suggest that there is a risk of hepatotoxicity when taking therapeutic doses of acetaminophen ( $\leq 4$  g/day). None of the presently available databases and monitoring systems are adequate to answer questions about dose, intentionality, causality, or the nature of trends in cases of serious adverse events with OTC and prescription products.

- The case series and databases that FDA cites as support for proposed labeling recommendations have serious methodological weaknesses. In nearly all instances, it is not possible to determine the true dose of acetaminophen ingested or the patient's true intent at the time acetaminophen may have been ingested. Causality cannot be determined from these data, which do not contain a control group and likely contain biases including referral and ascertainment bias.
- Analyses performed by McNeil using updated information from databases reviewed by FDA indicate that cases of acetaminophen overdose, acetaminophen-associated hepatotoxicity, and acetaminophen-associated death, whether intentional or unintentional, are not increasing.
  - The number of acetaminophen-related emergency room visits decreased from 2000 through 2004 compared with 1993 through 1999 (NHAMCS).
  - In the years since 1999 when ICD-10 codes were initiated, the rate of age-adjusted acute liver failure (ALF) mortality and acetaminophen-associated ALF mortality have not shown an increasing trend (MCOB).
  - Poison control center calls for unintentional ingestion of acetaminophen products have remained stable since 2000 (TESS).
  - A stable pattern of reporting was observed for hepatic events involving OTC acetaminophen products as a suspected drug in non-suicide cases during the years 2004 through 2006 (AERS).
- Hospitalization rates for ALF in the United States (US) from 1999 through 2006 have been fairly stable and the percentage of ALF cases that are transplanted or are waiting for a transplant that may be secondary to acetaminophen overdose is very low.
- McNeil strongly urges FDA, in collaboration with other stakeholders, to identify new ways to evaluate the risk of serious adverse events with OTC and prescription products, designed to have the sensitivity to reliably measure the impact, if any, of the changes to a product's label and educational initiatives.

- Since such a high percentage of consumers currently report using acetaminophen-containing products according to the package instructions, it is unlikely that the databases that FDA has historically used have the ability to detect meaningful changes, even when they occur, in consumer behavior. In addition, changes in consumer behaviors may not translate into an observable decrease in the number of cases of hepatotoxicity.
- New systems need to be designed to obtain reliable information on targeted events (eg, unintentional overdose).

### **1.3.3 McNeil's Assessment of Liver Safety and Acetaminophen Metabolism**

The experimental and clinical data that FDA reviewed and cited in FDA's proposed rule were incomplete, and these and other available data do not support the supposition of risk of acetaminophen hepatotoxicity in individuals with liver disease at therapeutic doses.

McNeil has analyzed the literature published through April 2007 and several clinical metabolism studies on acetaminophen, including a recently completed McNeil-sponsored metabolism study in adults with liver disease, which directly address issues raised at the 2002 NDAC meeting. The experimental and scientific data that McNeil presents are counter to the hypothesis of risk of acetaminophen hepatotoxicity in liver disease and with alcohol use.

- Suppositions (hypotheses) that might have made sense at one point in the history of the voluminous acetaminophen literature are no longer tenable when newer findings and insight are taken into account, particularly in light of new and more sophisticated evidence of the role of critical cytochrome P450 isoforms, hepatocellular glutathione homeostasis, and glucuronyl- and sulfotransferase systems.
- True depletion of hepatic glutathione, defined as an intracellular concentration below 10% of normal (the critical point at which mitochondria become susceptible to oxidative stress), has not been documented in humans aside from states of intoxication by some drugs, including excessive overdoses of acetaminophen.
- Suppositions that adults with liver disease may be at risk due to differences in glutathione concentrations or CYP2E1 activity are often based on considering changes to each system involved in activation or detoxification in isolation. There is

a failure to recognize that both glutathione concentrations and CYP2E1 activity can change in the same direction in a given condition, including advanced liver disease.

- Experimental and clinical data show that glucuronidation is preserved in liver disease with evidence that UGT may be up-regulated in the remaining viable cells. Although experimental research on sulfation is sparse and does not differentiate among etiologies of liver disease, data from seven acetaminophen metabolism studies unequivocally show that the amounts of glucuronide and sulfate metabolites produced are the same as those in healthy adults. Again, the changes that have been observed do not result in detectable enhanced risk.

#### **1.3.4 New and Published Acetaminophen Metabolism Studies**

New data confirm that stable chronic liver disease, in the presence or absence of alcohol, does not pose a risk for developing hepatotoxicity at therapeutic doses of acetaminophen and that the proposed labeling text, “Ask a doctor before use if you have liver disease” is not warranted. New and more sophisticated evidence of the role of critical cytochrome P450 isoforms (CYP2E1), hepatocellular glutathione homeostasis, and glucuronyltransferase systems show that the suppositions regarding risk in individuals with liver disease are theoretical in nature. These experimental and scientific data do not support the hypothesis of a risk of acetaminophen hepatotoxicity in individuals with liver disease at the maximum-labeled daily dose. Importantly, data do not support the idea that individuals with liver disease need to take lower maximum daily doses of acetaminophen.

- New and published metabolism data do not show either “decreased deactivation and/or increased metabolic activation of acetaminophen in the diseased liver”. The amount of thiol metabolites (a marker of NAPQI formation) is similar in individuals with and without liver disease, demonstrating no decrease in glutathione conjugation (decreased deactivation) or increase in metabolism by CYP2E1 (increased metabolic activation) in individuals with liver disease.
  - The amounts of thiols produced are similar after single doses or after repeat dosing of acetaminophen at 4 g/day in individuals with and without liver disease.
  - The metabolic formation clearance of thiol metabolites is similar in the diseased liver after a single dose, and it does not change after repeat dosing of acetaminophen 4 g/day for four days.

- New metabolism data from a McNeil-sponsored study show that acetaminophen metabolism increases with the administration of the maximum labeled daily dose of acetaminophen for four days in individuals with diseased and healthy livers. Consecutive daily dosing of acetaminophen induces glucuronidation (a nontoxic metabolic pathway), resulting in increased total body clearance of acetaminophen and increased production of the glucuronide metabolite.
- New and published pharmacokinetic data show that individuals with liver disease have a modest increase in the elimination half-life of acetaminophen (about 1 to 2 hours on average) that does not lead to progressive plasma accumulation of acetaminophen after repeat dosing or to a change in the amount metabolized via CYP2E1 compared with healthy individuals. While total body clearance is about 15 to 60% lower on average, which reflects slower acetaminophen removal, this is not relevant to the biotransformation to metabolites, which is essentially the same as that in healthy adults.
- Safety data from five prospective clinical studies of subjects with liver disease of varying severity and etiology show no evidence of acetaminophen hepatotoxicity at therapeutic doses.
- Hepatologists and gastroenterologists often prefer acetaminophen use by patients with liver disease over nonsteroidal anti-inflammatory drugs (NSAIDs). Indeed, acetaminophen is commonly used to treat flu-like symptoms associated with interferon treatment in hepatitis C patients.

### ***1.3.5 Use of Acetaminophen in Individuals Who Consume Alcohol***

An alcohol warning on acetaminophen-containing products as it relates to therapeutic doses of acetaminophen is not warranted. New clinical safety data from multiple prospective, randomized, double-blind, placebo-controlled trials demonstrate that alcoholics can safely take the current maximum labeled daily dose of acetaminophen (4 g/day). As such, FDA's proposed labeling that "severe liver damage may occur if you take 3 or more alcoholic drinks every day while using this product" is inappropriate because it suggests that there is a risk when taking the current maximum labeled daily dose of acetaminophen.

- New clinical safety data not available at the time of FDA's 2002 NDAC meeting from multiple prospective, double-blind, randomized, placebo-controlled trials

demonstrate that alcoholics can safely take the current maximum labeled daily dose of acetaminophen (4 g/day).

- These studies make it no longer appropriate for FDA to use historical, methodologically-flawed, retrospective reports of acetaminophen overdose cases to support proposed labeling recommendations, specifically designed to communicate information to consumers about the effects of taking recommended doses of acetaminophen ( $\leq 4$  g/day).
  - FDA's new warning is inconsistent with known and theorized acetaminophen metabolism in the presence of alcohol.
- Alcohol use negatively affects decision-making, impairs judgment and memory, decreases risk perception, mars the ability to respond appropriately to potential threats, and is associated with an increased risk of death from virtually any type of injury.
    - The association of alcohol and acetaminophen-induced injury, such as acute liver failure, is related to risky behaviors that lead to acetaminophen overdose, such as not reading and following acetaminophen dosing instructions, taking more than the recommended dose, suicide behavior, and not getting quick medical attention following an acetaminophen overdose.
    - It is very likely that the reported association among alcohol, acetaminophen, and hepatotoxicity is related to acetaminophen overdose rather than to physiological conditions or metabolic alterations of acetaminophen metabolism in alcoholics.
- Some data suggest that alcohol use may be a risk factor for taking more than the recommended dose (overdose) of acetaminophen and the development of hepatotoxicity. Therefore, if FDA deems that a new or reformatted alcohol warning is necessary, this warning should reflect the most current scientific data and apply only to taking more than the recommended dose (overdose), not therapeutic doses ( $\leq 4$  g/day).
  - Data do not support reducing the current maximum labeled daily dose of acetaminophen (4 g/day) for individuals who consume any amount of alcohol.

#### **1.4 McNeil Comments on Educational Initiatives**

McNeil agrees that, in addition to scientifically appropriate labeling, concurrent consumer and healthcare professional education may help to minimize misuse of OTC analgesic products. McNeil remains committed to creating, sponsoring and providing ongoing consumer and healthcare professional education focused on addressing intentional and inadvertent consumer misuse behaviors. Since 2002, McNeil has developed, supported and implemented educational initiatives aimed at focusing OTC medication users on:

- product ingredients
- 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 (e.g., NSAIDs) during the same time period
- the importance of recognizing that all medications have risks, particularly when more than the recommended dose is taken

McNeil has implemented educational initiatives through a variety of media (eg, TV, print, radio) and through partnerships with professional and advocacy organizations.

## **2 EXECUTIVE SUMMARY ITEM 2: MCNEIL'S RESPONSE TO FDA'S REQUEST FOR COMMENTS AND DATA**

### **2.1 Efficacy and Safety of Acetaminophen**

The ability of consumers to self-treat pain with acetaminophen and reliably obtain adequate pain relief depends upon the continued availability of OTC acetaminophen-containing products that are labeled at the current maximum single dose, 1000 mg, as well as at the current maximum daily dose, 4000 mg per day. Data from clinical trials demonstrate that 1) the 1000 mg single dose is needed to provide adequate analgesia and antipyretic efficacy, as well as duration of effect, across the entire population, compared with the 500 or 650 mg dose; and 2) that the current maximum labeled daily acetaminophen dose of 4000 mg per day has a favorable safety profile.

Historically, OTC internal analgesics have been available in a range of doses to facilitate a consumer's choice based on their needs and preferences. Based on the data, acetaminophen should not only continue to be available as 1000 mg (extra-strength) dosed every 4 to 6 hours up to 4000 mg per day but also as 650 mg (regular-strength) dosed

every 4 hours up to 3900 mg per day, and as 1300 mg (extended-release) dosed every 8 hours up to 3900 mg per day. It would be inappropriate for FDA to arbitrarily mandate that a consumer seeking pain relief or fever reduction should be denied the opportunity to use the most effective dose of acetaminophen, that is appropriate for the individual circumstances and needs, when it has been demonstrated that acetaminophen can be safely used at the maximum labeled daily dose (4 g/day). Data from controlled clinical trials support continuing the current monograph dosing of OTC acetaminophen: a maximum of 1000 mg per dose and a maximum daily dose of 4000 mg.

- More than 150 clinical trials conducted over five decades document the efficacy and safety of acetaminophen at currently labeled doses as a pain reliever and fever reducer.
  - Data from randomized, double-blind, placebo-controlled, single-dose clinical trials demonstrate that acetaminophen 1000 mg provides significantly better analgesia and antipyresis in the general population, compared to the 500 mg or 650 mg dose; the duration of effect of acetaminophen 1000 mg is also longer than the duration seen with acetaminophen 500 mg or 650 mg.
  - Pharmacokinetic-pharmacodynamic (PK-PD) modeling shows that acetaminophen 1000 mg consistently exceeds or approaches the plasma concentration needed for 50% of maximum analgesic effect (EC<sub>50</sub>), whereas acetaminophen 650 mg does not. By analogy, acetaminophen single doses lower than 650 mg would have a lesser effect that would not reasonably be expected to be clinically meaningful throughout the general population.
- Multiple-dose clinical trials demonstrate that the current maximum labeled daily dose of acetaminophen (3900 to 4000 mg per day) provides significantly better analgesic efficacy, compared with lower doses, and that this analgesic effectiveness is sustained over time.
  - Data from controlled clinical trials demonstrate that acetaminophen is well-tolerated with a favorable safety profile across the approved dose range up to 4000 mg per day.
- Medical professional association guidelines recommend acetaminophen use up to 4000 mg per day. Additionally, acetaminophen is recommended as the OTC analgesic of choice for specific subpopulations at risk for NSAID-associated gastrointestinal, cardiovascular or renal adverse effects.

### **2.1.1 Dosage for People who Consume Alcohol**

Data do not support reducing the current maximum labeled daily dose of acetaminophen (4 g/day) for patients who consume any amount of alcohol. New clinical safety data from multiple prospective, double-blind, randomized, placebo controlled trials demonstrate that alcoholics can safely take the current maximum labeled daily dose of acetaminophen (4 g/day).

An alcohol warning on acetaminophen-containing products as it relates to therapeutic doses of acetaminophen is not warranted.

### **2.1.2 Combinations with Methionine or N-Acetylcysteine (NAC)**

McNeil agrees that there are insufficient data to mandate that all acetaminophen-containing products, including OTC and prescription medicines, be formulated with either methionine or NAC. There is no evidence that such a requirement would prevent or reduce hepatotoxicity associated with either intentional or unintentional acetaminophen overdose. Adverse effects, occasionally serious, have been reported with both methionine and NAC. Because only rarely do consumers take a dose that reaches the potential threshold for toxicity, mandating that all products be formulated with methionine or NAC, in the hope of preventing or reducing hepatotoxicity in the small segment of consumers who overdose on acetaminophen, would unnecessarily expose the vast majority of the population to potential adverse effects of methionine or NAC.

- Methionine and NAC are effective antidotes for preventing and treating toxicity following acute acetaminophen overdose.
  - There are very limited data documenting the safety of products combining acetaminophen and methionine, and no data documenting the safety of products combining acetaminophen and NAC.
  - If acetaminophen is only available in combination with methionine or NAC, large numbers of people will be unnecessarily exposed to methionine or NAC, which themselves have the potential for adverse effects.
  
- The cost of a combination acetaminophen and methionine or NAC product would be substantially greater than that of acetaminophen alone.
  - Given the widespread use of acetaminophen in the US the increased costs of a combination product would increase cost to the consumer and

healthcare system. The increased costs would make acetaminophen less accessible to those who could not afford the more costly product.

### **2.1.3 Package Size and Package Configuration Restrictions**

In 1998, new legislation in the United Kingdom (UK) mandated package size restrictions for OTC acetaminophen and aspirin tablet products. In the UK, the tablet formulations of most OTC analgesics are currently marketed in blister packages. Insufficient data are available to require restrictions on package size or restrictions on package configuration (eg, blister packages) for acetaminophen and other OTC analgesics in the US. There are no data indicating a benefit of package size or package configuration restrictions for unintentional overdose.

- The results of studies that have attempted to assess the effect of package size restrictions for acetaminophen in the UK are not consistent regarding the effect of the 1998 legislation on reducing intentional overdose. There were no data indicating a benefit of package size restrictions on unintentional overdose.
- Restricting acetaminophen availability in countries other than the UK failed to have an appreciable effect on acetaminophen overdose.
- Mandating package size restrictions or blister packages only for acetaminophen in the US would likely result in consumers switching to analgesics with a less favorable safety profile for everyday use, so that any such restrictions would have to be applied to all OTC analgesics.
- Mandating package size restrictions or blister packages for any or all OTC analgesics in the US would likely result in:
  - Increased cost and burden for consumers and the healthcare system,
  - Difficulty with the use of blister packages for some consumers (eg, elderly, individuals with arthritis), and
  - A significant burden to individuals with chronic pain conditions.

### **2.1.4 Considerations About Acetaminophen Use in Other Selected Subpopulations**

Data do not support that individuals with human immunodeficiency virus (HIV), malnutrition or fasting states, or Gilbert's syndrome develop hepatotoxicity following ingestion of therapeutic doses of acetaminophen. A label warning for individuals with HIV, malnutrition

or fasting states, or Gilbert's syndrome who take acetaminophen at the maximum labeled daily dose is not necessary.

Any purported increased susceptibility to acetaminophen-induced hepatotoxicity in individuals with these conditions, that may or may not affect acetaminophen metabolism, is purely hypothetical and unsubstantiated by data.

#### *2.1.4.1 Use of Acetaminophen in HIV-Positive Individuals*

- The data do not support that survival in HIV-infected individuals is negatively affected by the use of acetaminophen at the current maximum labeled daily dose.
- The use of therapeutic doses of acetaminophen in HIV-infected individuals does not affect steady-state plasma glutathione concentrations.

#### *2.1.4.2 Use of Acetaminophen in Malnutrition or Fasting States*

- A few retrospective case reports and case series allege an association between acetaminophen-induced hepatotoxicity and fasting. The terms "malnutrition" and "fasting" are inconsistent across, and poorly defined within, these case reports.
  - Case information for these reports is lacking, making it impossible to independently confirm nutritional status and causality.
- Importantly, a prospective clinical study that evaluated the effect of fasting in humans on acetaminophen metabolism found no evidence for a shift from glucuronidation to oxidation of acetaminophen following calorie restriction.

#### *2.1.4.3 Use of Acetaminophen in Gilbert's Syndrome*

- Individuals with Gilbert's syndrome have a defect in UDP-glucuronosyltransferase isozymes, UGT1A1.
- Glucuronidation of acetaminophen is by UDP-glucuronosyltransferase isozymes UGT1A6 and UGT1A9, not UGT1A1, the affected isozymes in Gilbert syndrome.
- Acetaminophen metabolism studies in adults with Gilbert's syndrome show little or no reduction in glucuronidation capacity for acetaminophen metabolism.

- The only study in patients with Gilbert's syndrome that has shown an increase in the proportion of glutathione-derived metabolites did not show the increase to be clinically meaningful.
  - No published data are available to suggest that plasma or hepatic glutathione is lower in patients with Gilbert's syndrome.
- In an analysis of 112 patients with liver failure due to an acute acetaminophen overdose (mean dose 28.5 g), the UGT1A1\*28 homozygosity associated with Gilbert's syndrome did not influence the severity or outcome of acute liver or multi-organ failure.

**3 EXECUTIVE SUMMARY ITEM 3: MCNEIL'S RESPONSE TO FDA'S PROPOSED LABELING FOR OTC NON-STEROIDAL ANTI-INFLAMMATORY DRUG (NSAID) PRODUCTS**

Item 3 of McNeil's submission responds to FDA's proposed labeling for OTC NSAID products. McNeil agrees with FDA's statements [71 FR 77315] that ibuprofen and other OTC analgesics:

- are generally recognized as safe and effective OTC analgesics when labeled appropriately and used as directed,
- benefit millions of consumers every year for the intermittent treatment of minor aches and pains and fever, and
- should continue to be accessible to consumers in the OTC setting.

McNeil fully implemented all labeling changes for its OTC ibuprofen products by January 2006, pursuant the June/July 2005 OTC NSAID supplemental labeling templates issued by FDA. Therefore, all currently marketed McNeil OTC ibuprofen products are in compliance with FDA's proposed rule. Although McNeil asserts that the current labeling for all OTC NSAID products is adequate for safe consumer use, McNeil recommends that consumers with existing liver disease may benefit from more explicit labeling language that encourages them to seek advice from a doctor prior to taking any OTC NSAID products.

As noted throughout the NSAID sections of FDA's proposed rule, serious renal events following NSAID therapy almost always occur in patients with preexisting renal dysfunction, congestive heart failure, or compromised hepatic function. McNeil asserts that individuals

in this latter subset population may benefit from more explicit label language similar to current language for those with heart or kidney disease. The addition of liver disease under the “Ask a doctor before use if you have” warning so that the bullet reads, “heart, kidney, or liver disease” provides additional important instruction for a consumer with liver disease.

The scientific data presented in Items 1 and 3 of McNeil’s response to FDA’s proposed rule indicate that use of NSAIDs in consumers with existing liver disease requires caution while use of acetaminophen at therapeutic doses does not. Acetaminophen can be used safely in adults with liver disease and is preferred to aspirin and other NSAIDs in this subpopulation because of the increased renal sensitivity and gastrointestinal bleeding risk in this subset population. If consumers with preexisting liver disease are directed on acetaminophen labeling to seek advice from their doctor prior to use but these same consumers are not provided a similar, explicit caution on OTC NSAID labeling, the potential for inadvertent consumer use of OTC NSAIDs, without the benefit of consultation with a doctor, may increase in this subset population.