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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

[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.

number of excess deaths was calculated as follows. Estimates for the upper and lower 95% confidence interval were calculated in the same manner.

- 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

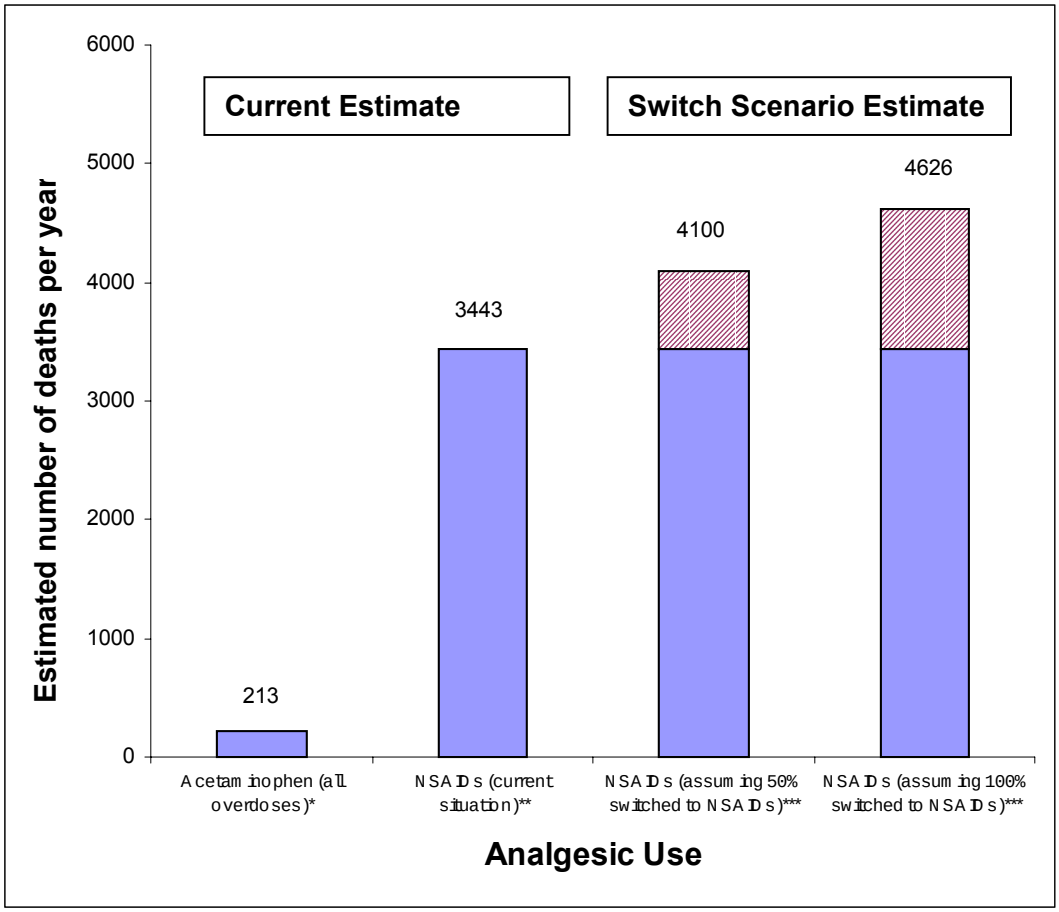
Hepatotoxicity with acute liver failure following very large overdoses is the most prominent serious adverse event associated with acetaminophen. Although there are no surveillance programs or national statistics, one personal unverified estimate is that 2000 individuals develop acute liver failure annually 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].

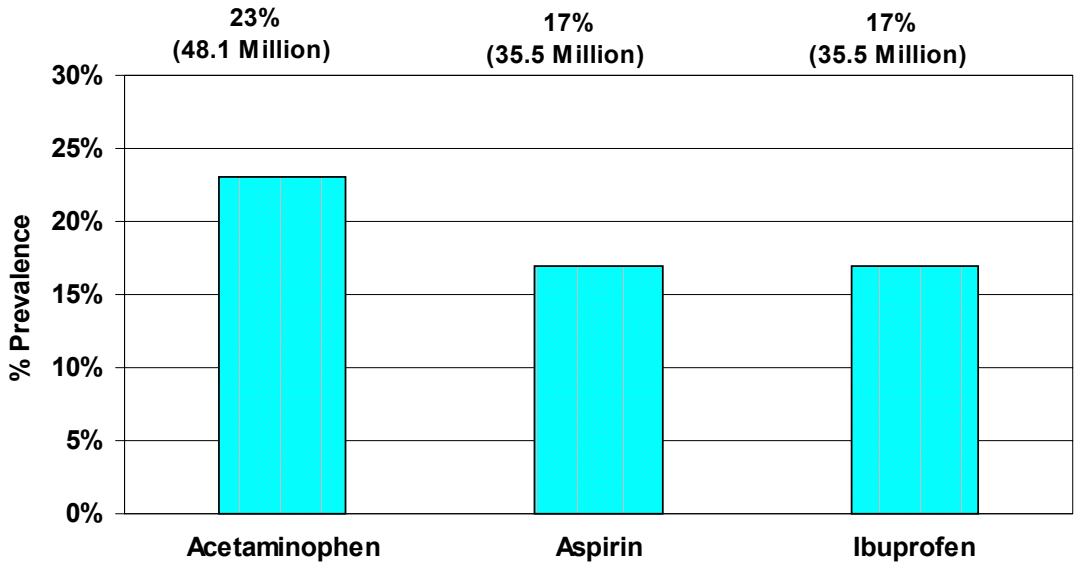
National Council on Patient Information and Education (NCPIE) Survey - a market research telephone survey of consumers and health professionals to track their opinions about the use of OTC medicines. The survey was conducted between October 25 and November 11, 2001 and consisted of two polls: one of 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.

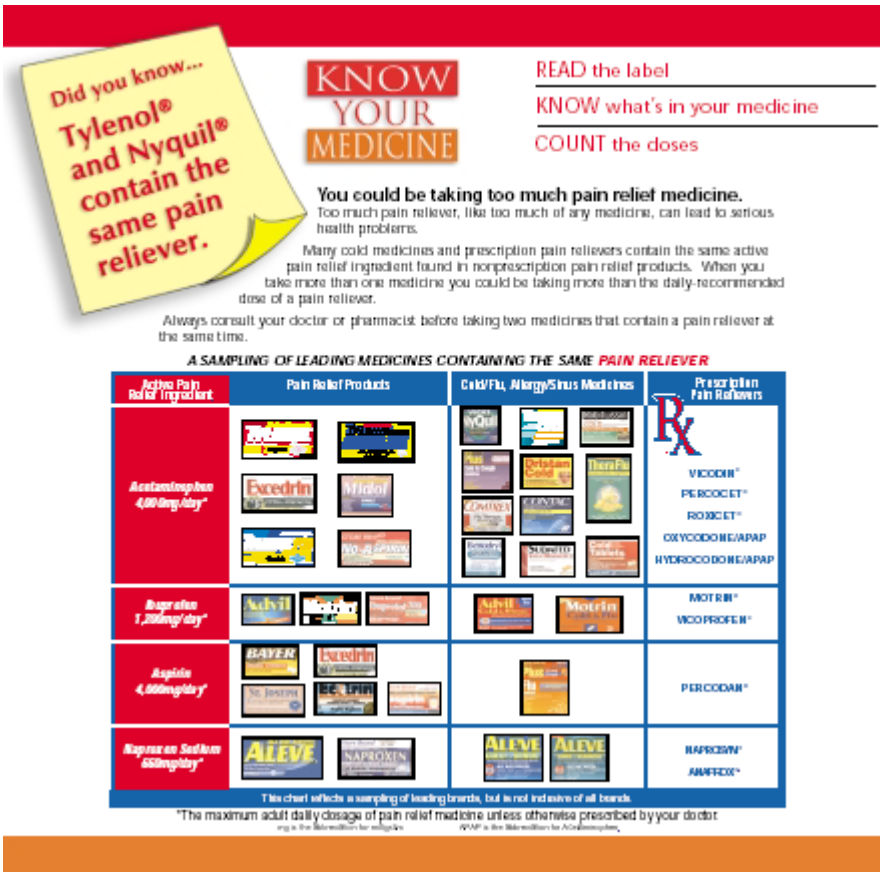
Examples of specific activities related to the "Know Your Medicine" initiative include the following:

- 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.

5 REFERENCE LIST

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