ITEM 2: MCNEIL'S RESPONSE TO FDA'S REQUEST FOR COMMENTS AND DATA

1 INTRODUCTION

In Section XIV of FDA's proposed rule, the Agency indicates that, in addition to requesting general comments on the proposed amendment, it is seeking comment on specific issues. McNeil has provided comments in this section and throughout Item 1 and Item 3.

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2 OTHER APPROACHES TO REDUCE UNINTENTIONAL OVERDOSE

2.1 FDA Comments from the Proposed Rule

In Section XIV. Request for Comments of FDA's proposed rule, FDA requests comment on: "Appropriate approaches to reduce unintentional acetaminophen overdose." [71 FR 77346]

2.2 McNeil's Comments

McNeil agrees with FDA's proposal that, in addition to appropriate labeling, concurrent consumer and healthcare professional education may help to minimize misuse of OTC products, including acetaminophen-containing products. McNeil has taken a leadership role in developing and implementing multiple large-scale collaborative educational programs that have reached tens of millions of consumers and healthcare professionals. These programs have focused on how consumers can responsibly use OTC products, including acetaminophen-containing products.

As mentioned in Item 1, Section 8 of this submission, McNeil has implemented labeling changes for its OTC analgesic products aimed at focusing the attention of consumers on the product ingredients, the proper dosing and use of medications, the importance of not taking more than the recommended dose, and the importance of not using two products, either prescription or OTC, containing identical ingredients. Additionally, McNeil has petitioned the FDA to expand dosing directions on OTC pediatric acetaminophen product labeling to include children under two years of age.

As mentioned in Item 1, Section 8 of this submission, in 2004 McNeil launched a "Responsible Use of Medicine" educational campaign targeting adults, caregivers of children, and healthcare professionals. This enduring, multi-year educational campaign aims to encourage proper dosing of Tylenol acetaminophen products through a variety of media and influencers. To complement this campaign, McNeil has also partnered with the American Academy of Family Physicians (AAFP) and the American Pharmacists Association (APhA) to more widely and effectively deliver messages regarding safe and appropriate use of OTC medicines to consumers and healthcare professionals. McNeil continues to support these programs.

McNeil remains committed to developing, supporting, and implementing labeling and educational initiatives directed to consumers, caregivers of children, and healthcare

professionals and focusing attention on consumer misuse behaviors involving OTC acetaminophen-containing products that may contribute to overdose. 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. Finally, McNeil passionately urges FDA to respond to McNeil's outstanding Citizen Petition requesting that the dosing directions on OTC pediatric acetaminophen product labeling be expanded to include children under 2 years. McNeil is committed to continue working with FDA and other stakeholders to encourage the appropriate use of OTC products, including acetaminophen-containing products.

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3 MORE SPECIFIC DIRECTIONS FOR ACETAMINOPHEN

3.1 FDA Comments from the Proposed Rule

In Section XIV, Request for Comments of FDA's proposed rule, FDA requests comment on the following issue: "Whether more specific directions, such as those currently required for OTC drug products containing ibuprofen, should be considered for acetaminophen." [71 FR 77346]

3.2 Background

The **Drug Facts** for single-ingredient adult OTC drug products containing ibuprofen state the following directions:

Directions

- **Do not take more than directed**
- **The smallest effective dose should be used**
- Do not take longer than 10 days, unless directed by a doctor (see Warnings)

Adults and children 12 years and older	• Take 1 [dosage form] every 4 to 6 hours while symptoms persist • If pain or fever does not respond to 1 [dosage form], 2 [dosage form] may be used • Do not exceed 6 [dosage form] in 24 hours, unless directed by a doctor
Children under 12 years	• Ask a doctor

The **Drug Facts** for single-ingredient adult OTC drug products containing acetaminophen state the following directions

Directions

- **Do not take more than directed (see overdose warning)**

Adults and children 12 years and over	• Take 2 [dosage form] every 4 to 6 hours while symptoms last • Do not take more than x [dosage form] in 24 hours • Do not use for more than 10 days, unless directed by a doctor
Children under 12 years	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

3.3 McNeil's Comments

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[1], 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 daily acetaminophen dosage of 4000 mg/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 medical 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

[1] According to the Tentative Final Monograph (TFM) for OTC Internal Analgesic, Antipyretic, and Antirheumatic (IAAA) drug products, the current maximum allowable single adult dose for acetaminophen products is 1000 mg, not to exceed 4000 mg per day (53 FR 46204).

8 hours up to 3900 mg per day[2]. 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 consumer's circumstances and needs, when it has been demonstrated that acetaminophen can be safely used up to the maximum labeled daily dose (4000 mg per 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.

3.4 Key Points from McNeil's Response

- More than 150 clinical trials conducted over five decades document the efficacy and safety of acetaminophen at currently labeled dosages 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_{50}), 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 currently labeled maximum 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 at dosages up to 4000 mg per day.
- Medical 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] Marketed under approved New Drug Application (NDA)

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4 EFFICACY AND SAFETY OF ACETAMINOPHEN

Acetaminophen has been available as an over-the-counter (OTC) analgesic and antipyretic in the US since 1955. The efficacy of acetaminophen has been clearly established in a multitude of controlled, single- and multiple-dose clinical studies. The safety profile of therapeutic doses from these clinical studies and from actual consumer experience demonstrates a long record of safety and tolerability.

In this section, the efficacy and safety of therapeutic doses of acetaminophen, as demonstrated in controlled clinical trials, will be reviewed. Data supporting the therapeutic importance of the current maximum allowable single dose, 1000 mg[1], and the current maximum allowable daily dose, 4000 mg per day, in treating mild-to-moderate pain will be presented.

4.1 FDA Comments from Proposed Rule

In Part A, Safe and Effective Daily Acetaminophen Dose, of Section VII of FDA's Proposed Rule [71 FR 77335], FDA states, "The current information on unintentional overdose suggests that the margin of safety may be less than originally determined." FDA further states, "If the at risk subpopulations cannot be identified, or addressed through appropriate labeling, and cases of liver injury continue to be reported, FDA may reconsider whether the labeled maximum daily dose is still generally recognized as safe and effective for use in the general population."

4.2 McNeil's Position

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[1], 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

[1] According to the Tentative Final Monograph (TFM) for OTC Internal Analgesic, Antipyretic, and Antirheumatic (IAAA) drug products, the current maximum allowable single adult dose for acetaminophen products is 1000 mg, not to exceed 4000 mg per day (53 FR 46204).

dose; and 2) that the current maximum daily acetaminophen dosage of 4000 mg/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 medical 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[2]. 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 consumer's circumstances and needs, when it has been demonstrated that acetaminophen can be safely used up to the maximum labeled daily dose (4000 mg per 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.

4.3 Key Points from Clinical and Safety Data

- More than 150 clinical trials conducted over five decades document the efficacy and safety of acetaminophen at currently labeled dosages 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_{50}), 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.

[2] Marketed under approved New Drug Application (NDA)

- Multiple-dose clinical trials demonstrate that the currently labeled maximum 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 at dosages up to 4000 mg per day.
- Medical 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.

4.4 Benefits of the Appropriate Acetaminophen Dosing in the Self-Management of Pain

Pain is pervasive among US adults: 89% experience pain at least once a month, approximately half report continuous or intermittent pain that last longer than three months, and 42% experience pain on a daily basis [1,2]. Individuals experiencing pain almost always rely on self-management in the form of OTC analgesics [3]. The availability of effective OTC analgesics for the treatment of pain allows consumers to make a decision to self-manage pain in a safe and cost-effective manner, especially in situations where immediate access to a healthcare provider may be limited.

Pain is an almost ubiquitous experience. Among the most common painful conditions are headaches, minor pain of arthritis, low back pain, muscle pain, menstrual pain and neck pain and these conditions form the basis for the OTC analgesic indication. For decades, acetaminophen has been a mainstay among choices available to consumers seeking pain relief or fever reduction. As shown in this document, acetaminophen 1000 mg has clear evidence of effectiveness in treating a variety of painful conditions; the acetaminophen maximum daily dose of 4000 mg (and dosages above this, as well) has been prospectively shown to be efficacious and to have an excellent safety profile. Additionally, data from controlled clinical trials involving different pain states and data from meta-analyses demonstrate the superior efficacy of 1000 mg compared with lower doses [15-18, 112, 123-129].

Under-treatment of pain can result in considerable costs to individuals (eg, the deterioration of physical and psychological health), families (eg, increased social isolation and caregiver distress), employers, and the US healthcare system (eg, substantial healthcare utilization

and costs) [4-11]. Limiting the ability of consumers to adequately self-treat pain by compromising the effectiveness of acetaminophen by either decreasing the current allowable maximum single dose, 1000 mg, or the current allowable maximum daily dose, 4000 mg, may have a significant negative impact on patients, families, employers, and even the US healthcare system. By way of example, a 2004 study, sponsored by the Consumer Healthcare Products Association and conducted by Northwestern University, determined that the use of OTC medication in the treatment of upper respiratory infections saves the U.S. healthcare system and economy $4.75 billion annually [12].

4.5 Efficacy in Adults: Controlled Clinical Studies

In 1977, the Advisory Review Panel on OTC Internal Analgesic, Antipyretic and Antirheumatic (IAAA) Drug Products concluded that acetaminophen was a safe and effective OTC analgesic for adults when taken at the maximum allowable single dose of 1000 mg, not to exceed 4000 mg in 24 hours. This same dose was reaffirmed in 1988, when FDA published the Tentative Final Monograph (TFM) for OTC IAAA Drug Products.

In addition to the Agency's formal acknowledgement of acetaminophen's safety and efficacy on these two occasions, a significant body of clinical study data has prospectively documented the efficacy of acetaminophen as an OTC analgesic and antipyretic in adults and children. The published literature and McNeil's internal studies include more than 150 placebo-controlled trials that have proven acetaminophen's efficacy in a variety of pain models: dental pain, tension headache/migraine, osteoarthritis, menstrual pain, muscle aches and pains, fever, and other painful conditions. This section provides more specific information about these studies and about the range of acetaminophen doses that have been examined, all of which support McNeil's position that maintaining the current maximum allowable single dose, 1000 mg, as well as at the current maximum allowable daily dose, 4000 mg per day, is needed to provide adequate analgesia and antipyretic efficacy, as well as duration of effect, across the *entire* population.

4.5.1 Dental Pain

Seventy-three studies demonstrated the significant analgesic efficacy of acetaminophen, compared to placebo, in a dental pain model [13-85]. The dose of acetaminophen studied ranged from 325 mg to 2000 mg, with the majority of studies using 1000 mg.

4.5.2 Muscle Pain

One study by Schachtel demonstrated a significant effect of acetaminophen 650 mg, compared to placebo, in the relief of myalgia in subjects with febrile upper respiratory tract infections and muscle pains [86].

4.5.3 Headache

Fifteen single-dose studies demonstrated the significant effect of acetaminophen, compared to placebo, in treating headache pain [87-101]; thirteen of these studies examined acetaminophen 1000 mg; two studies [87,91] examined acetaminophen 650 mg and 648 mg, respectively.

Four other clinical studies demonstrated the significant effect of acetaminophen 1000 mg, compared to placebo, in the treatment of migraine [102-105].

4.5.4 Adult Menstrual Cramps

Two studies demonstrated the superior efficacy of acetaminophen 2600 mg per day [106] and 4000 mg per day [107], compared to placebo, in relieving menstrual pain.

4.5.5 Adult Fever

Four studies [86, 108-110] demonstrated the significant effect of acetaminophen 650 mg and two studies [111,112] demonstrated the significant effect of acetaminophen 1000 mg, compared to placebo, in treating fever in adults.

4.5.6 Osteoarthritis Pain

The safety and efficacy of acetaminophen at current maximum allowable single dose, 1000 mg and the current maximum allowable daily dose, 4000 mg/day has been demonstrated in multiple osteoarthritis studies [113-122].

The safety and efficacy of acetaminophen for treating osteoarthritis pain for greater than ten days under the direction of a healthcare provider has been demonstrated in ten placebo- or NSAID-controlled osteoarthritis trials involving approximately 2900 patients [113-122]. Acetaminophen's efficacy was consistently significantly better than placebo across these studies, in which the duration of treatment ranged from two to 52 weeks. Importantly, there were no reports of hepatotoxicity or hepatic failure among subjects taking the currently-labeled maximum daily dose of OTC acetaminophen for up to one year.

4.6 Multiple Studies in Different Pain States Demonstrate the Superior Efficacy of 1000 mg vs. either 650 mg or 500 mg

Data from controlled clinical trials involving different pain states and data from meta-analyses demonstrate the superior efficacy of 1000 mg compared with lower doses [15-18, 112, 123-129].

4.6.1 Individual clinical studies show that acetaminophen 1000 mg is a significantly more effective dose than 500 mg.

4.6.1.1 Pain

McNeil has conducted a new single-dose dental pain study that compared acetaminophen 1000 mg and 500 mg [15]. For the primary efficacy endpoint, Total Pain Relief over 4 hours, acetaminophen 1000 mg was significantly better than acetaminophen 500 mg ($p<0.0001$); this difference between 1000 mg and 500 mg translated to an approximate 42% greater pain relief. The time-action curve for pain relief showed that the 500 mg dose separated from placebo through four hours after dosing but not at Hours 5 and 6. By comparison, acetaminophen 1000 mg was significantly better than placebo for pain relief through Hour 6, the end of the observation period; at each observation time acetaminophen 1000 mg was also significantly better than acetaminophen 500 mg. A similar qualitative difference between the 500 mg and 1000 mg doses was seen for the other analgesic endpoints. The magnitude of this benefit of 1000 mg represents a robust and clinically important benefit.

Three other controlled clinical dental pain studies also demonstrate the superior efficacy of acetaminophen 1000 mg, compared to acetaminophen 500 mg [16-18].

Quiding et al conducted a double-blind, randomized, placebo-controlled dental pain study comparing codeine 60 mg, acetaminophen 500 mg and acetaminophen 1000 mg, for two doses for up to 10 hours [16]. One hundred and eight subjects were included in the analysis. For pain relief, both 500 mg and 1000 mg were superior to placebo and acetaminophen 1000 mg, which provided a 55% reduction in pain, was superior to 500 mg, which provided a 30% reduction in pain, after a single dose. This separation continued after the second dose.

Nystrom et al conducted a double-blind, randomized, dental pain study comparing a single dose of diflunisal 500 mg to two doses of acetaminophen 500 mg and 1000 mg [17]. One hundred thirty-two subjects were included in the analysis. Acetaminophen 1000 mg, which provided a 36% reduction in pain, was superior to acetaminophen 500 mg, which provided a 10% reduction in pain, after a single dose. This separation continued after the second dose. The mean duration of pain relief was 4.6 hours for 1000 mg and 3.3 hours for acetaminophen 500 mg.

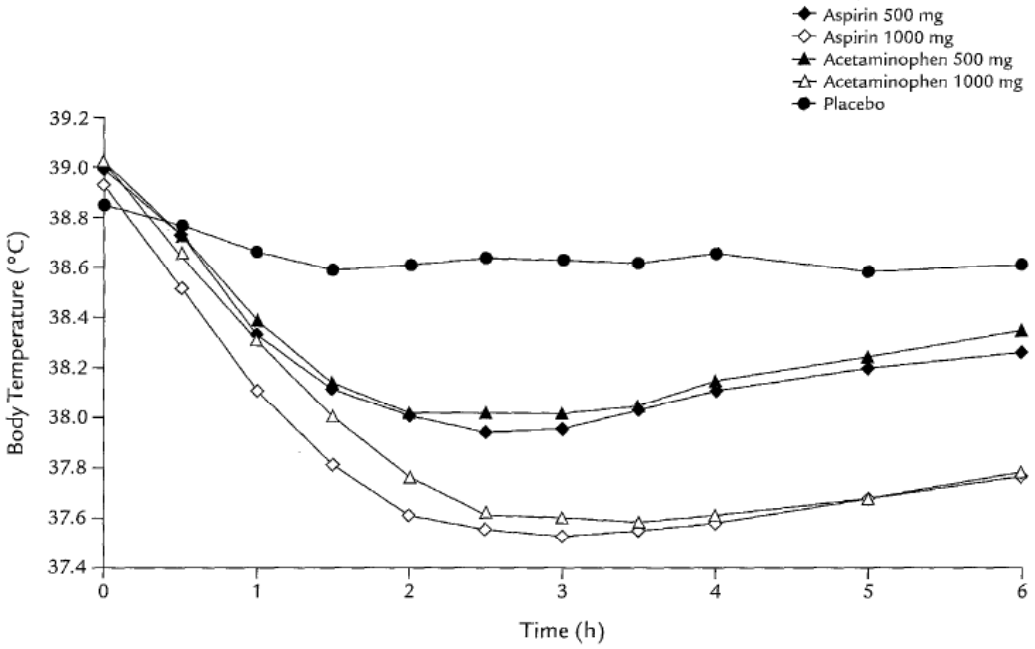
Seymour et al conducted a double-blind, randomized, placebo controlled dental pain study comparing ketoprofen 12.5 mg and 25 mg, and acetaminophen 500 mg and 1000 mg [18]. Two hundred subjects were included in the analysis, with 40 subjects in each of the acetaminophen groups. Both acetaminophen doses provided significantly superior pain relief (AUC 0-360) compared to placebo. Acetaminophen 1000 mg was numerically better than the 500 mg dose, however this difference did not reach statistical significance.

Two other studies, one in post-orthopedic surgery pain [123] and one in experimentally-induced painful conditions [124], also demonstrated superior efficacy of acetaminophen 1000 mg, compared to acetaminophen 500 mg, for various analgesic measures.

4.6.1.2 Fever

A randomized, double-blind placebo-controlled study in febrile respiratory infection found quantitatively better fever reduction among subjects treated with acetaminophen 1000 mg, compared to those who were treated with acetaminophen 500 mg, as shown in Figure 4.1, excerpted from Bachert et al [112].

Figure 4.1 Antipyretic time course of single doses of acetaminophen and aspirin 500 mg and 1000 mg



4.6.2 Individual clinical studies show that acetaminophen 1000 mg is a significantly more effective dose than 650 mg.

Two placebo-controlled studies that specifically compared acetaminophen 1000 mg and 650 mg and demonstrated that 1000 mg is a more effective dose than 650 mg [125,126]. These studies, however, were not included in either of the meta-analyses described below.

Hopkinson et al conducted a single-dose, double-blind, randomized, placebo-controlled episiotomy pain study among 263 subjects, comparing acetaminophen 650 mg and 1000 mg [125]. For pain relief, onset of relief, and subject global evaluation, both acetaminophen 650 mg and 1000 mg were superior to placebo and acetaminophen 1000 mg was superior to acetaminophen 650 mg.

Yuan et al. conducted a single-dose, double-blind, randomized, placebo-controlled induced pain (cold-pressor test) study comparing acetaminophen 325 mg, 650 mg and 1000 mg [126]. Eighteen subjects were studied. Only the 1000 mg dose was statistically superior to placebo.

4.6.3 Meta-Analyses Show that Acetaminophen 975/1000 mg is a Significantly More Effective Dose Than 600/650 mg.

Three publications describe two meta-analyses comparing the relative efficacy of various acetaminophen doses (600/650 mg and 1000 mg). These analyses quantified efficacy using the concept of "number-needed-to-treat (NNT)" although this calculation is not a traditional endpoint in analgesic studies [127-129]. The NNT was defined as the number of subjects required to receive a particular acetaminophen dose in order for one subject to achieve at least 50% pain relief at that dose, compared with placebo, over a four- to six-hour treatment period. The more effective the acetaminophen dose, the lower the NNT.

McQuay et al identified 40 randomized, placebo-controlled clinical trials of subjects with moderate-to-severe postoperative pain evaluated over four to six hours, evaluating the 1000 mg dose [127]. As shown in Table 4.1, the NNT for acetaminophen 1000 mg is 3.7 and the NNT for acetaminophen 600/650 mg is 5.4, demonstrating a 33% improvement in efficacy of 1000 mg compared to 600/650 mg. McQuay et al concluded that the appropriate dose of acetaminophen for post-operative pain was 1000 mg.

Table 4.1 Meta-Analysis Results for Single-Dose Efficacy of Acetaminophen1000 mg and 600/650 mg Compared with Placebo [127]

	At least 50% pain relief with		
	Acetaminophen	Placebo	
	N	N	NNT
Dose (mg)	(%)	(%)	(95% CI)
1000	701/1527	197/1032	3.7 (3.3 - 4.3)
	(46)	(19)	
600/650	250/614	131/593	5.4 (4.2 - 7.4)
	(41)	(22)	

A meta-analysis by Barden et al [128] includes reports of randomized, double-blind, placebo-controlled clinical trials of subjects with postoperative pain of moderate-to-severe intensity evaluated over a four- to six-hour treatment period.

As shown in Table 4.2, the NNT for acetaminophen 975/1000 mg is 3.8 and the NNT for acetaminophen 600/650 mg is 4.6, demonstrating a 22% improvement in efficacy of 1000 mg compared to 650 mg [128].

Table 4.2 Meta-Analysis Results for Single-Dose Efficacy of Acetaminophen 975/1000 mg and 600/650 mg Compared with Placebo [128]

	At least 50% pain relief with		
	Acetaminophen	Placebo	
	N	N	NNT
Dose (mg)	(%)	(%)	(95% CI)
975/1000	746/1627	222/1132	3.8 (3.4 - 4.4)
	(46)	(20)	
600/650	358/954	145/932	4.6 (3.9 - 5.5)
	(38)	(16)	

These data demonstrate that acetaminophen 975-1000 mg has superior analgesic efficacy, compared to 600-650 mg. There is a clear, meaningful dose response: the 975-1000 mg dose has 22-33% greater efficacy, compared to 600-650 mg.

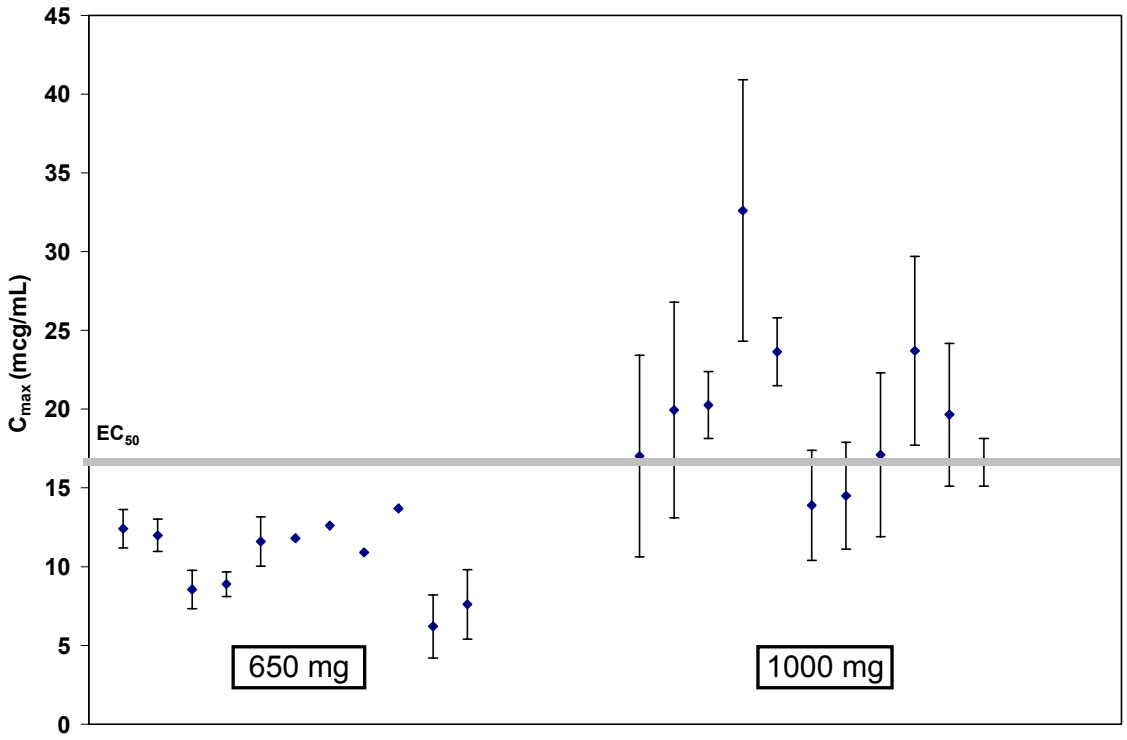
4.6.4 PK Modeling Demonstrates Acetaminophen 1000 mg Peak Plasma Concentrations Exceeds EC50 Whereas Acetaminophen 650 mg Does Not

Based on pharmacokinetic-pharmacodynamic (PK-PD) modeling, acetaminophen 1000 mg yields significant peak plasma concentrations that consistently meet or exceed the EC_{50} (concentration in the effect compartment that elicits 50% of the maximum drug response) [130, 131]. These PK-PD results are consistent with the meta-analyses of acetaminophen [127-129] and with individual placebo-controlled studies [15-18, 112, 123-126] that report numerically or statistically significantly greater efficacy of acetaminophen 1000 mg, compared with lower doses.

A population PK-PD model was developed using data from 114 subjects in dental pain studies, who received a single dose of acetaminophen 1000 mg (either caplet or effervescent solution) or placebo [130]. Another PK-PD model used data obtained from male patients in a dental pain study coupled with data obtained in a separate a PK study [131]. Both models found that, similar to other orally-administered analgesics, the initial analgesic effect of acetaminophen lags behind the increase in plasma concentration, so an effect compartment model was used to link the pharmacokinetic and pharmacodynamic data. Estimates of the pharmacodynamic parameters obtained for acetaminophen analgesia were very similar in both models: the EC_{50} was 15.2 mcg/mL [130] and 16.55 mcg/mL [131].

To further assess the relationship among the 650 mg and 1000 mg doses, corresponding plasma concentrations, and the EC_{50}, McNeil examined single-dose pharmacokinetic data available from twelve published studies [132-143]. As shown in Figure 4.2, across these studies the mean acetaminophen C_{max} following a 1000 mg dose consistently approached or exceeded the two separately-calculated EC_{50}s noted above (ie, 15.2 mcg/mL and 16.55 mcg/mL), whereas the 650 mg dose did not. By analogy, doses lower than 650 mg would be predicted to be even less effective. This demonstrates that 1000 mg is the most appropriate single analgesic dose, and provides a pharmacologic rational to maintain the current maximum allowable single dose, 1000 mg.

Figure 4.2 Acetaminophen Cmax for 650 mg and 1000 mg Doses Demonstrate that 1000 mg Consistently Attains the Plasma Concentration Needed for 50% Maximum Relief



4.7 Acetaminophen Dosing Interval

Because pain and fever may last longer than the effective duration of any OTC analgesic/antipyretic, the dosing interval can be as highly relevant to an individual as the dose taken at each occasion. Both pharmacokinetic and clinical data support the continuing appropriateness of the four- to six-hour dosing interval for acetaminophen.

Multiple pain studies reviewed above have demonstrated that 1000 mg provides significantly greater analgesic efficacy than either 650 mg or 500 mg. The duration of analgesic action of acetaminophen 1000 mg involving subjects with moderate to severe pain levels is approximately 4-6 hours, while the duration for acetaminophen 650 mg is approximately 4 hours. Operationally, this is consistent with the dosing interval for acetaminophen.

4.8 Safety of Acetaminophen

A review of multiple-dose acetaminophen clinical studies indicates that at the current maximum single dose, 1000 mg, and the current maximum daily dosage, 4000 mg, acetaminophen is well-tolerated and has a favorable safety profile.

4.8.1 Short-term Clinical Trials

Acetaminophen 1000 mg has been administered under controlled conditions for 2–10 days to treat a variety of conditions, including oral surgery pain [18, 64, 70, 82], arthritis pain [144], fever [145], muscle aches and pains [146], dysmenorrhea [107], and other painful conditions [147,148]. These studies demonstrate that acetaminophen is well-tolerated and not associated with serious adverse events.

Although discussed in greater depth in Item 1, Section 3 of this submission, it is noteworthy to point out that McNeil sponsored a prospective, randomized, multiple-dose pharmacokinetic study of three-days' treatment with acetaminophen 4, 6, and 8 g/day in healthy subjects (N = 37) [149]. This study found no clinically relevant elevation in ALT or AST levels following dosages of up to twice the currently-approved daily maximum. Acetaminophen pharmacokinetics was also noteworthy, in that glucuronidation was induced at all three dosages. As will be seen elsewhere in this submission, this has important positive implications for the short-term tolerability of supratherapeutic doses of acetaminophen in adults [150].

4.8.2 Longer-term Clinical Trials

Acetaminophen's tolerability in longer-term use has been demonstrated in osteoarthritis trials similar to situations of physician supervised care involving a total of 2,922 patients [113-122]. Daily acetaminophen dosages of up to 4000 mg per day were taken. The duration of use ranged from three weeks [113] to twelve months [121] and, taken together, demonstrated no evidence of hepatotoxicity, hepatic dysfunction, or hepatic failure. These data support that, even at durations substantially exceeding the ten-day OTC maximum, acetaminophen up to 4000 mg per day is well-tolerated.

Long-term clinical trials in patients with osteoarthritis found no evidence of hepatic failure [151-154]. A randomized study involving 571 adults with osteoarthritis who took acetaminophen 4000 mg per day for twelve months found no evidence of hepatic failure; hepatic dysfunction; aminotransferase levels ≥ 2 times the upper limit of normal reference range; renal failure; or serum creatinine levels ≥ 1.5 times the upper limit of the reference range [152].

Another randomized study evaluated the safety of acetaminophen extended-release 650 mg and 1300 mg, given three times daily for three months for the treatment of moderate to moderately-severe osteoarthritis of the hip or knee among 483 adults [154]. No subject in this clinical trial exhibited a progressive increase in liver function tests.

A randomized, three-month study evaluated sustained-release acetaminophen 3900 mg per day in 542 subjects with hip or knee osteoarthritis of the hip or knee [151]. There were seven participants that had abnormal ALT or AST levels, however in four cases liver function tests approached or returned to normal with continuing acetaminophen treatment and in the other three cases there were confounding circumstances that could have influenced liver enzymes. In no case was this acetaminophen dosage associated with liver failure or dysfunction.

4.9 Acetaminophen: Professional Treatment Guidelines

Medical Associations and health care professionals recommend acetaminophen up to 4000 mg per day to treat pain in the general population, as well as in patient groups who may be at an increased risk of NSAID-associated adverse events.

- The American College of Gastroenterology recommends the use of acetaminophen for the general population, as well as for patients with ulcers and individuals with chronic pain from arthritis and other causes [155].
- The National Kidney Foundation in their 1996 position statement recommends acetaminophen as the non-narcotic single analgesic of choice for episodic use in patients with underlying renal disease [156].
- Acetaminophen is also the pain reliever of choice in women who are pregnant [157].
- The American College of Rheumatology recommends acetaminophen for first-line symptomatic treatment of hip and knee pain in patients with osteoarthritis [158].
- The Agency for Healthcare Research and Quality [159] and the American Pain Society [160], have consistently recommended acetaminophen, up to a maximum of 4000 mg per day, as the first choice in drug therapy for the treatment of osteoarthritis.
- The American Heart Association has developed a stepped care approach for the management of musculoskeletal symptoms in patients with cardiovascular disease or at risk for ischemic heart disease [161]. When pharmacologic treatment is necessary, acetaminophen or aspirin is recommended as first-line therapy. For patients with a history or risk for gastrointestinal (GI) bleeding, acetaminophen is the preferred initial drug of choice. Acetaminophen is also the analgesic of choice in individuals who use aspirin for cardioprotection, since it does not influence platelet aggregatation or interfere with the antithrombotic effects of aspirin [162]. When taken with aspirin, acetaminophen has not been shown to contribute to gastrotoxicity, nor interfere with inhibition of platelet aggregation.

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5 ACETAMINOPHEN DOSING IN PEOPLE WHO CONSUME ALCOHOL

5.1 FDA Comments from the Proposed Rule

In Section XIV. Request for Comments of FDA's proposed rule, FDA requests "both comment and data on specific dosage for safe and effective use of acetaminophen in people who consume alcohol." [71 FR 77346]

5.2 McNeil Position

Data from controlled clinical trials demonstrate that acetaminophen is well-tolerated with a favorable safety profile at doses up to 4 g/day. 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.

5.3 McNeil Data and Comments

- More than 150 clinical trials conducted over five decades document the efficacy and safety of acetaminophen at currently labeled doses up to 4 g/day as a pain reliever and fever reducer. For full discussion of these data, please refer to Item 2, Section 4.
- 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). For a full discussion of these data, please refer to Item 1, Section 7.

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6 COMBINATIONS WITH METHIONINE OR N-ACETYLCYSTEINE (NAC)

6.1 FDA Comments from the Proposed Rule

Within the December 26, 2006 Proposed Rule, FDA states that it is currently evaluating different safety measures to reduce the relative risk for hepatotoxicity with the use of acetaminophen. One suggested theoretical method by which hepatotoxicity might be reduced is to administer acetaminophen in combination with methionine or N-acetylcysteine (NAC). However, FDA notes that, in a review of the literature from 1975 to December 2002, they did not find any studies that specifically address whether either combination would prevent liver toxicity. Furthermore, FDA notes that, while a combination product containing acetaminophen 500 mg and methionine 100 mg is marketed in the United Kingdom (UK), there are no available data on the relative efficacy or the prophylactic antidotal dose of methionine for protecting the liver after acetaminophen overdose in humans. FDA concludes that, at the present time, there is insufficient evidence that combinations of acetaminophen with methionine or NAC would prevent or reduce acetaminophen-induced liver toxicity and asked that comments and data on this issue be provided to the agency.

6.2 McNeil's Position

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 minority of consumers who overdose on acetaminophen, would unnecessarily expose the vast majority of the population to potential adverse effects of methionine or NAC.

6.3 Key Points from McNeil's Response

- There is no evidence that combining acetaminophen with methionine or NAC in any product, OTC or prescription, would prevent or reduce hepatotoxicity associated with either intentional or unintentional acetaminophen overdose.
- The overwhelming majority of consumers using acetaminophen-containing products in the US do not take more than maximum daily dose of acetaminophen (4 g/day). Only rarely do consumers take a dose that reaches the potential threshold for toxicity.
- Methionine and NAC are effective antidotes for preventing and treating toxicity following acute acetaminophen overdose.
- Adverse effects, occasionally serious, have been reported with both methionine and NAC.
    - 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.
    - Since the overwhelming majority of consumers do not exceed the maximum daily dose of acetaminophen (4 g/day), exposing all consumers of acetaminophen-containing products to methionine or NAC would subject them unnecessarily to possible safety risks without providing them with any benefit.

- 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.

6.4 Acetaminophen Overdose

Each year tens of millions of consumers in the US use acetaminophen-containing products. Only a small number of these individuals exceed the maximum daily dose of acetaminophen (4 g/day). The tens of millions of consumers who use acetaminophen as

directed, benefit from its analgesic and antipyretic effects and are not at risk for hepatotoxicity due to acetaminophen overdose.

Individuals who take an acetaminophen overdose are at risk for developing hepatotoxicity. Following an *acute acetaminophen overdose* (an ingestion of a toxic amount of acetaminophen within a period of eight hours or less), the risk of hepatotoxicity can be decreased by the timely administration of antidotes such as methionine or NAC [1,2,3,4,5,6,7,8,9,10]. Theoretically, it might be useful to combine an antidote, such as methionine or NAC, with acetaminophen so that if an excessive overdose is taken, the antidote is already in a person's body [11]. In order for such an approach to be effective, especially with respect to intentional overdose by suicidal individuals, an antidote would need to be added to all acetaminophen formulations [12]. There is insufficient evidence that combination products containing acetaminophen and methionine or acetaminophen and NAC would prevent or reduce acetaminophen-induced hepatotoxicity. Furthermore, since the overwhelming majority of consumers do not exceed the maximum daily dose of acetaminophen (4 g/day), exposing all consumers of acetaminophen-containing products to methionine or NAC would subject them unnecessarily to possible safety risks without providing them with any benefit.

6.5 Acetaminophen and Methionine Combination

6.5.1 Rationale for Acetaminophen and Methionine Combination

Methionine, also referred to as L-methionine, is an essential amino acid. The recommended daily allowance of methionine for adults is 13 mg/kg or about 1 g per day. Methionine has a role in the synthesis of numerous compounds including proteins, homocysteine, cysteine, glutathione, taurine, sulfate, S-adenosyl-methionine (SAM), D-glucose, and glycogen. While the D-isomer of methionine is not involved in the synthesis of these compounds, like the L-isomer, it has antioxidant activity.

Clinical studies show that hepatotoxicity may be prevented by administering methionine within 10 hours of an acute acetaminophen overdose [1,2,3,8]. Methionine is thought to prevent acetaminophen-induced hepatotoxicity by preventing glutathione depletion during an overdose through promotion of glutathione synthesis [13,14,15]. The antioxidant activity of methionine itself, as a well its chelating ability and free-radical scavenging activity, may also play a role in its hepatoprotective effects [13].

As early as 1974, it was suggested that the addition of methionine to acetaminophen products may have the potential to prevent or reduce hepatotoxicity following an acute acetaminophen overdose [11]. To date only one acetaminophen methionine combination product remains available in the UK (Paradote®; acetaminophen 500 mg, methionine 100 mg). Pameton®, a product containing 500 mg of acetaminophen and 250 mg of methionine, was withdrawn from pharmacy sales in the UK in 1997 due to concerns that an excessive intake of methionine may be associated with an increased risk of cardiovascular disease [16].

6.5.2 Data Supporting Protective Efficacy of Acetaminophen-Methionine Combination

Animal studies show that administration of methionine before or following a hepatotoxic dose of acetaminophen, as well as SAMe, can prevent and reduce acetaminophen-induced liver damage[14,17,18,19]. McNeil is unaware of any prospective studies involving the administration of established hepatotoxic doses of acetaminophen to humans in an attempt to determine if methionine administered either before acetaminophen overdose or concurrently with acetaminophen overdose prevents or reduces hepatotoxicity. Furthermore, there are no published case reports describing overdoses with an acetaminophen and methionine combination product. Therefore, currently there is no human evidence that formulating any acetaminophen-containing product with methionine actually prevents or reduces acetaminophen hepatotoxicity and what effect, if any, such a product would have on cases of intentional and unintentional acetaminophen overdose.

6.5.3 Safety of Methionine

If the addition of methionine to every nonprescription and prescription acetaminophen product in the US was required, the vast majority of consumers who use acetaminophen according to labeled directions and do not take more than the recommended dose (overdose) would have no choice but to take acetaminophen in combination with methionine. They would be unnecessarily exposed to methionine. Importantly, the safety of a combination product containing acetaminophen and methionine should be clearly established. There are numerous concerns regarding the safety of methionine. Consequently, use of a combination product containing methionine could have important public health consequences.

There are very limited published data examining the safety of a combination of acetaminophen and methionine. In one clinical study that included 53 subjects, drowsiness was more common in subjects who received two to four sachets per day of a combination

of acetaminophen and methionine than in those who received an equivalent amount of acetaminophen alone [17]. In another clinical study that enrolled 30 subjects, drowsiness was more common in subjects who received two to four sachets per day of a combination of acetaminophen and methionine than in those who received placebo [18]. In both of these studies, treatment was administered for three days. Each sachet contained 1073 mg paracetamol-N-acetyl-DL-methionate (equivalent to 500 mg acetaminophen) and 500 mg of free acetaminophen.

There are no published data examining the safety of the combination of acetaminophen and methionine beyond three consecutive days, whereas there are much more published data available on the safety of methionine monotherapy. In general, these data suggest that methionine doses of up to 250 mg daily are well tolerated [13]. However, there may be safety concerns with administration of higher doses.

Because methionine is metabolized to homocysteine, an increase in methionine intake may be associated with an increase in homocysteine concentrations [19]. Atherosclerotic changes have been observed in animals fed methionine-enriched diets [20]. Vascular endothelial dysfunction has been observed in humans administered 100 mg/kg of oral methionine [21,22]. Although numerous observational studies have associated increased homocysteine levels with coronary heart disease and stroke [23,24,25,26], multiple prospective studies that evaluated the impact of homocysteine-lowering therapies on cardiovascular outcomes did not demonstrate an effect on vascular events [27,28,29]. Yet, there remains concern that methionine supplementation may have the potential to increase the risk of cardiovascular disease [13]. In the UK, a combination product containing acetaminophen and methionine 250 mg was withdrawn from pharmacies due to concerns regarding an increased risk of cardiovascular disease [16].

In the course of studying the relationship between plasma homocysteine and cardiovascular disease, thousands of individuals have been administered methionine loading tests in which a methionine dose of 100 mg/kg body weight is administered and then homocysteine levels are measured [19]. The administration of methionine in this manner has been associated with an acute increase in homocysteine levels, vascular endothelial dysfunction, and transient complications that impair perception and vigilance. The transient complications include sleepiness, nausea, polyuria, and decreased or increased blood pressure [30]. There is one report of a death following the administration of a methionine-loading test, however, indirect evidence suggests that the individual received an overdose of methionine, a dose approximately 70 times the dietary requirement [31].

Concern regarding the ingestion of methionine by pregnant women has been raised. In one case control study, women who had children between the ages of one and five years with nonsyndromic orofacial clefts had significantly higher homocysteine plasma levels than controls when fasting and after a standardized oral methionine loading test [32]. Data from observational studies also suggest that hyperhomocysteinemia may be associated with placental related diseases, such as pre-eclampsia, spontaneous abortion, and placental abruption [33]. The PDR for Nutritional Supplements states the following: "L-methionine supplements should be avoided by pregnant women and nursing mothers unless they are prescribed by a physician" [13]. Acetaminophen is the preferred analgesic in pregnant woman, especially in the first trimester, so a combination product with methionine would carry more risk.

Data from one case control study suggest that a diet rich in methionine, salt and nitrite may be associated with an increased risk of gastric cancer [34]. This finding is consistent with animal data that suggest that methionine promotes intestinal carcinogenesis [35] as well as vitro data demonstrating that in the presence of salt and nitrite methionine is mutagenic [36]. The PDR for Nutritional Supplements notes that there is some epidemiological data suggesting a link between increased dietary methionine and increased risk of gastric cancer but more research is necessary [13].

In rats, a decrease in rhabdomyosarcoma pulmonary metastases was observed in animals fed a diet with reduced methionine content [37]. In Yoshida sarcoma-bearing mice, methionine depletion was associated with tumor regression [38]. The PDR for Nutritional Supplements has the following related precaution: "L-methionine supplementation should be avoided by those with neoplastic disease", and states that there is some preliminary data to suggest that a high intake of dietary methionine may promote some cancers [13].

High doses of methionine have been associated with numerous adverse events, including nausea, vomiting, reduced serum folate levels, a reduction in red blood cell count, an increase in white blood cell count, changes in serum pH and potassium levels, and increased urinary calcium excretion [1,2,8,13,39,40]. In patients with schizophrenia, daily administration of large doses of methionine (ie 40g/day) has been associated with the development of functional psychosis [41], and in patients with cirrhosis, a large single dose of methionine-precipitated encephalopathy [42]. The PDR for Nutritional Supplements has the following related precaution: "Supplemental L-methionine should be used with great caution in those with schizophrenia and those with hepatic and renal failure" [13].

Other safety concerns with use of methionine have been reported. In patients with bipolar disorder, use of SAM for treatment of depression has been associated with anxiety, mania, and hypomania [43]. In women on a low-protein diet, dietary supplementation with L-methionine was associated with a reduction in glycine levels [44]. The PDR for Nutritional Supplements states that L-methionine use is contraindicated in individuals with homocystinuria and those hypersensitive to any components of a methionine-containing product [13].

If all OTC and prescription products containing acetaminophen were mandated to contain methionine, consumers who use acetaminophen according to labeled directions and do not overdose would be unnecessarily exposed to methionine. Numerous potential safety concerns with use of methionine indicate that unnecessary broad exposure is not appropriate.

6.5.4 Determining the Correct Dose of Methionine for an Acetaminophen and Methionine Combination Product

The recommended daily allowance of methionine as an essential amino acid is approximately 1 g per day [13]. When methionine is used in the treatment of an acute acetaminophen overdose, the recommended cumulative methionine dose is 10 g administered as four 2.5 g doses [1,2,3]. While a weight ratio of methionine to acetaminophen as low as 10% protected against hepatotoxicity in rats, the current product available in the UK uses a ratio of 20% [12]. There is not enough information to determine accurately the dose of methionine to combine with acetaminophen that may prevent or reduce hepatotoxicity following acetaminophen overdose.

6.6 Acetaminophen and N-Acetylcysteine (NAC)

6.6.1 Rationale for Acetaminophen and N-Acetylcysteine Combination

Currently, there is no commercially available product combining NAC with acetaminophen. NAC is an N-acetyl derivative of the amino acid L-cysteine. It is metabolized to cysteine, one of the precursors of glutathione [45]. NAC therapy is accepted as the standard of care for patients at risk of acetaminophen-induced hepatotoxicity following an acute acetaminophen overdose based on the Rumack-Matthew nomogram and is also administered to patients with acetaminophen-induced hepatotoxicity and fulminant hepatic failure. It is well accepted that NAC is beneficial in preventing acetaminophen-induced hepatotoxicity following acute acetaminophen overdose and decreasing morbidity and mortality in patients with acetaminophen-induced hepatotoxicity and fulminant hepatic failure [5,4,6,7,46,47,48].

Numerous mechanisms have been proposed for how NAC prevents and reduces hepatotoxicity following an acetaminophen overdose. Since NAC is metabolized to cysteine, it prevents glutathione depletion through promotion of glutathione synthesis [49]. NAC is also thought to protect the liver by providing thiol groups that bind directly with NAPQI. NAC may also act as an antioxidant and convert NAPQI back to acetaminophen [4,46].

6.6.2 Data Supporting Protective Efficacy of Acetaminophen-NAC Combination

Animal studies have demonstrated that the administration of NAC before or following administration of a hepatotoxic dose of acetaminophen can prevent and reduce acetaminophen-induced hepatotoxicity [50]. McNeil is unaware of any prospective studies involving the administration of established hepatotoxic doses of acetaminophen to humans in an attempt to determine if NAC administered either before acetaminophen or concurrently with acetaminophen prevents or reduces hepatotoxicity. McNeil is also unaware of a combination NAC and acetaminophen product that is commercially available outside the US.

6.6.3 Safety of NAC

If the addition of NAC to every OTC and prescription acetaminophen product was required in the US, the vast majority of consumers who use acetaminophen according to labeled directions and do not take more than the recommended dose (overdose) would be unnecessarily exposed. Importantly, the safety of such a combination product containing acetaminophen and NAC should be clearly established.

Because there are no published data examining the safety of a combination of acetaminophen and NAC, the published safety data examining the adverse effect profile of NAC when used as monotherapy for the treatment of acute acetaminophen overdose were reviewed. When NAC is used orally for the treatment of acute acetaminophen overdose, nausea and vomiting are commonly reported [46,51]. While anaphylactoid reactions, including angioedema, have also been reported with orally administered NAC, they are much more common with intravenous NAC [46,51]. Consequently, before exposing all individuals who consume acetaminophen to NAC, the incidence of anaphylactoid reactions with an acetaminophen and NAC combination product would need to be studied carefully.

If all products containing acetaminophen were to also contain NAC, people who used acetaminophen according to labeled directions would be unnecessarily exposed to NAC. Due the risk of anaphylactoid reactions, such unnecessary exposure is not appropriate.

6.6.4 Determining the Correct Dose of NAC for an Acetaminophen and NAC Combination Product

When oral NAC is used in the treatment of an acute acetaminophen overdose, a loading dose of 140 mg/kg is followed by 17 doses of 70 mg/kg every four hours [5,51]. When used by the intravenous route, the approved dose of NAC for the acute treatment of acetaminophen overdose is a 150 mg/kg loading dose followed by 50 mg/kg over four hours and then 100 mg/kg over 16 hours [9,10]. There are no published studies in humans examining the dose of NAC to be combined with acetaminophen. At this time, there is not enough information to determine accurately the dose of NAC to combine with acetaminophen to prevent or reduce hepatotoxicity following acetaminophen overdose.

6.7 Mandating that All Acetaminophen-Containing Products Contain Methionine or NAC Would Substantially Increase Costs

In the UK, combination products containing acetaminophen and methionine cost four to six times more than products containing acetaminophen alone [15]. While there are currently no commercially available products that combine acetaminophen and NAC, based on the cost of the acetaminophen and methionine combination product in the UK, one would expect that the cost of a product containing acetaminophen and NAC would be greater than that of a product containing acetaminophen alone. Given the widespread use of acetaminophen in the US, this could result in a significant increase in healthcare costs both for consumers and for the healthcare system. Furthermore, the increase in cost would make acetaminophen less accessible to those who could not afford the more costly product.

6.8 Burden of Implementation

In order to derive the maximum benefit from a combined formulation product, methionine or NAC would need to be added to all acetaminophen products, both OTC and prescription, that contain acetaminophen alone or in combination with other drugs. Mandating that all acetaminophen-containing products be formulated with either compound would place an undue burden on manufacturers that is not justified, given the lack of data supporting the effectiveness of such a requirement. Additionally, the foul taste and smell of oral NAC, which are difficult to mask [51], would make it challenging to incorporate NAC into an acetaminophen combination product that is palatable and acceptable to consumers, especially children. Furthermore, adherence with combination products containing NAC may be limited due to difficulty in masking the foul taste and smell and required larger table size.

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7 PACKAGE SIZE AND PACKAGE CONFIGURATION RESTRICTIONS

Package size and package configuration (eg, blister packages) restrictions for over-the-counter (OTC) acetaminophen products have been implemented in countries such as the UK and Ireland in an effort to reduce acute acetaminophen overdose in adults, particularly those associated with suicides or suicide gestures. Available data from these countries evaluating the effect of limitations on package size and configuration are summarized in the following sections. Tabular summaries of studies included in the review conducted by McNeil are provided in Attachment 1.

7.1 FDA Comments from the Proposed Rule

In Section VII, Additional Issues for Consideration and Section XIV, Request for Comments of FDA's proposed rule, FDA has requested comment on "package size and package configuration limitations as a mechanism to increase safe use of acetaminophen products by reducing overdose. Comments should address the possible impact of such measures on unintentional and intentional overdose" [71 FR 77314 at 77337 and 77346].

7.2 McNeil's Position

In 1998, new legislation in the 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.

7.3 Key Points Supported by Scientific and Medical Data

- 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.

7.4 Studies of Acetaminophen Package Size and Package Configuration Limitations in the UK Show Inconsistent Results

On September 16, 1998, the UK introduced new legislation that limited the number of OTC tablets of acetaminophen to a maximum of 32 per sale (16 g) when purchased through a pharmacy (although up to 100 tablets were allowed at the discretion of the pharmacist) and 16 per sale (8 g) when purchased through other retail outlets. In addition, overdose warnings were required on packets and leaflets in packets. The rationale for package size restriction is based on the finding that acute intentional overdose in adults (suicide attempts or suicide gestures), particularly with acetaminophen, has been perceived as a major health problem in the UK [1,2,3]. As many cases of acute intentional acetaminophen overdose are impulsive [4] and availability appears to be a factor in choice of self-poisoning agent [5], it was theorized that limiting package size would reduce the number of acute intentional acetaminophen overdoses (suicide attempts or suicide gestures).

The effect of limiting package size and package configuration on reducing acetaminophen overdoses in the UK has been assessed by numerous investigators, with conflicting outcomes. A number of studies suggest that the introduction of package size restrictions had a positive impact on acute intentional acetaminophen overdose in the UK, including reductions in the rate of acetaminophen overdoses, number of tablets taken during overdose, hospitalizations or emergency department visits, acetaminophen-related hepatotoxicity, liver transplantation, and mortality [6,7,8,9,10,11,12,13,14]. The extent and duration of the benefits, however, vary considerably among the studies. Whereas decreases in severe acetaminophen overdoses immediately following the package size restriction legislation have been reported [6,8], Robinson et al [7] observed decreases in the estimated quantity of acetaminophen ingested, but no reduction in the number of severe acetaminophen overdoses. Although a decline in acetaminophen overdose was reported by Thomas and Jowett [10] from February to August 1999 versus the same time period during the previous year (40 and 52 patients, respectively), the

number of non-acetaminophen overdoses—consisting mainly of antidepressants, antipsychotics, and sedatives—increased from 64 to 72. Similarly, Hawton et al [12] observed a decrease in fatal acetaminophen overdoses during the three-year period, a decrease in nonfatal acetaminophen overdoses in the first year after restrictions but no reductions in the next two years, and an *increase* in nonfatal ibuprofen overdoses in the three years following the package restriction legislation. Moreover, although a decrease in mortality was observed by Morgan et al [13], the authors note that these decreases may be attributable to random variation in mortality rates. Indeed, decreases in mortality attributable to other drug poisonings were also observed over the same time period. This observation was supported by an interrupted time-series analysis conducted by Morgan et al [15], which demonstrated that a decrease in fatal poisoning associated with aspirin, antidepressants, as well as acetaminophen compounds, occurred during the period 1998 to 2004. This further supports the hypothesis that the observed decline in acetaminophen mortality may not be due to package size restriction, but rather to a wider trend in the reduction of drug-poisoning suicide. Notably, the package size restrictions did not reduce the number of acetaminophen tablets sold on an annual basis [9,12].

In addition, it should be noted that in 2001, Hawton et al reported on the number of suicides, undetermined deaths, and deaths resulting from accidental poisoning attributed to acetaminophen for three periods, the penultimate 12 months before legislation in the UK mandated package size restrictions, the 12 months before the change, and the 12 months after the change [9]. Hawton reported that the percent of deaths attributed to acetaminophen alone as 9.0%, 8.3%, and 7.0% for these three periods, respectively, suggesting that the reduction in the percent of deaths due to acetaminophen started before the legislation. Similarly in 2004, Hawton reported that the number of admissions for liver transplants due to acetaminophen poisonings in six liver transplant units as 369, 329, and 271 for the same three reporting periods as reported in 2001 [12]. This suggests that something other than package size restrictions, perhaps consumer education, was responsible for the initial decline in rates.

A recent study suggests that many stores in the UK do not adhere to the UK acetaminophen package size restriction legislation. In 2004, Greene and colleagues [16] found that 17 of 24 stores visited in south London did not enforce the package size restrictions. The authors of this study suggested that in the absence of evidence demonstrating that the restriction legislation is being followed, one cannot assume that the legislation is the primary reason for any observed decreases in acetaminophen overdose. An earlier review article on acetaminophen poisoning also noted poor compliance with the restrictions in 1999, ie, more than the restricted number of tablets

could be purchased [17]. In addition, it has been noted that consumers intent on committing suicide can easily visit multiple supermarkets and/or pharmacies to obtain large quantities of acetaminophen [17,18].

Multiple studies conducted in Scotland found that acetaminophen restrictions had no beneficial effect, and, in some cases, had a negative effect on admissions for acetaminophen poisoning, acetaminophen poisoning deaths, and the proportion of overdoses attributed to acetaminophen [19,20,21,22,23,24,25,26]. Bateman et al [27] did report reductions in hospital discharge after introduction of package size restrictions in Scotland; however, antidepressant overdose and opioid overdose and misuse increased over this same time period. In a subsequent analysis of data in Scotland by Bateman et al in 2006 [23], it was reported that mortality and the proportional use of acetaminophen in overdose had increased in Scotland after package size restrictions were introduced. In other studies, short-term reductions in acetaminophen-related toxicity or emergency admissions were recorded, although these trends reversed over time [25,28]. Moreover, there have been no changes in the number of patients referred to the Scottish Liver Transplantation Unit because of acetaminophen-induced liver failure during the 2.5 years following introduction of package restrictions [29].

The limitations of these studies, including lack of a consensus definition of acetaminophen overdose, sampling bias, limited evaluation period after introduction of the legislation, and failure to consider changes in overdose epidemiology with other drugs have been presented as barriers to interpretation of the results [30,31,32,33,34]. In addition, the observational nature of these studies makes it difficult to establish a causal link between package size restrictions and changes in the occurrence of acetaminophen overdose. Although not subject to restrictions in availability, reductions in antidepressant overdose have also been reported during the same time period [35]. Therefore, given the conflicting outcome data and limitations of the available reports, the evidence for public health benefit from OTC acetaminophen package size or package configuration restrictions is lacking.

7.5 Restricting Acetaminophen Availability Outside the UK Failed to Have an Appreciable Effect

Studies conducted in Ireland, Australia, Canada, and Denmark have evaluated the effects of changes in acetaminophen availability on acetaminophen overdose and its sequelae. The majority of these studies reported little or no impact on overdose as the result of changes in the availability of acetaminophen.

In 1997, the Irish Medicines Board introduced voluntary guidelines suggesting that non-pharmacy outlets should only sell emergency supplies of acetaminophen in a maximum pack size of 12 tablets and only one pack should be sold on each occasion. Subsequent studies evaluating acetaminophen overdose in Ireland failed to demonstrate a beneficial effect from package size restrictions [36,37]. Following the publication of these voluntary guidelines, hospital admissions attributed to acetaminophen overdose decreased by only 1.9% [36]. Moreover, a review of 2,020 cases of deliberate acetaminophen overdose reported to the National Poisons Information Center in Ireland failed to demonstrate a difference in the number of reported cases of acetaminophen overdose or the number of tablets of acetaminophen ingested during overdose observed before (1997) and after (1998) introduction of the voluntary pack size restrictions [37]. In 2003, mandatory restrictions were established to limit sales of acetaminophen on each occasion to blister packs of up to 12 tablets in non-pharmacy outlets and up to 24 tables in pharmacy outlets [38]. In 2007, it was reported that ten of 20 pharmacies visited, allowed a customer to exceed this limit [39].

In Australia, two manufacturers of acetaminophen were forced to recall acetaminophen-containing products because of a tampering threat. Recalls reduced the acetaminophen supply for two periods of over two months each in 2000. The data for acetaminophen overdose during these periods of acetaminophen restriction are conflicting [40,41]. A study in New South Wales found that reduced availability of acetaminophen had no effect on the incidence of calls to a poison information center or presentations to a toxicology service for acetaminophen poisoning. However, during the recall periods there was an increase in calls to the poison information center for ibuprofen poisoning and an increase in presentations to the toxicology service for aspirin poisoning [40]. In contrast, a study in Western Australia reported a decrease in hospital admissions for acetaminophen poisonings and no increase in other analgesic poisonings when acetaminophen availability was restricted [41].

Place-of-sale restrictions in Canada limited the sale of acetaminophen in doses > 325 mg or packages > 24 tablets to pharmacies only. In September 1999, these restrictions were lifted in several Canadian provinces and territories, thereby increasing the availability of acetaminophen. Analysis of hospital discharge data collected 1.5 years before and after lifting of the place-of-sale restrictions demonstrated that the increased availability of acetaminophen had no significant effect on the rate of reported hospitalizations related to acetaminophen overdose [42].

Prior to 1984, acetaminophen was available only through prescription in Denmark. Ott et al [43] explored the effect of the transition of acetaminophen from prescription to OTC

by examining hospital admission and cause of death data from the National Board of Health for the period of 1978 to 1986. Despite a 50-fold increase in acetaminophen sales reported over this time period, a relative decrease was observed in the number of hospital admissions and deaths from acetaminophen overdose.

One study [44] investigated the relationship between sales of acetaminophen and non-fatal acetaminophen overdoses or suicides in the UK prior to the 1998 package size restrictions and in France where restrictions were in place that limited the amount of acetaminophen that could be purchased. The authors reported strong correlations in both countries between sales and overdoses or suicides. Although this study also reports that morbidity and mortality were less frequent in France where there were restrictions, it has been noted that it is difficult to compare differences in morbidity and mortality between countries due to the variability in rates of acetaminophen self-poisoning by country [30]. No analysis was conducted comparing event rates before and after package size restrictions were put in place within a country, thus the results of this study are not useful in assessing the effect of package size restrictions.

7.6 Impact of Regulations on Intentional Versus Unintentional Overdose

The impetus of the acetaminophen restrictions in the UK was to reduce acute intentional overdose (suicide attempts or suicide gestures). Intent was not addressed in studies that assessed the outcomes of package size restriction.

7.7 Unintended Consequences of Acetaminophen Package Size and Package Configuration Limitations

It is important to consider the net benefit/risk proposition resulting from the introduction of acetaminophen package size and/or package configuration limitations. This is especially important given the fact that only rarely do consumers take a dose of acetaminophen that reaches the potential threshold for toxicity. Unintended consequences such as, increased cost and burden to consumers and the healthcare system, increased use of drugs with a less favorable safety profile, and specific burdens to certain patient populations (eg, elderly, individuals with arthritis or other chronic pain conditions) may result in an overall negative impact on consumers and the healthcare system.

Restrictions on acetaminophen use may result in a compensatory increase in overdoses with other more toxic drugs for which an antidote is not available, or lead to use of “overdose cocktails” that are more dangerous because of drug-drug interactions and multiple drug toxicities [10,45,30,32,46]. Such switches from acetaminophen use in

overdose have been documented for antidepressants, antipsychotics, sedatives, and ibuprofen [10,12]. Moreover, as sales for acetaminophen and aspirin decreased following package size restrictions, sales for ibuprofen increased [47]. Increased use of ibuprofen may result in an increase in the incidence of adverse gastrointestinal, cardiovascular, renal and other serious adverse effects.

Restricting package size and package configuration may cause an undue burden on the consumer. Because of the changes in packaging, the cost to obtain an equivalent number of tablets would increase [18,46,48]. Extra costs would be incurred by all consumers, the overwhelming majority of whom who do not misuse acetaminophen [46,48]. In addition, the smaller package size will necessitate more frequent trips to the stores and pharmacies to purchase acetaminophen, particularly among patients who require chronic therapy, such as those with arthritis [46]. Blister packs may become barriers to use in the elderly and in those with arthritis.

Lastly, package size restrictions may lead to less self reliance of the general public in managing their own healthcare and would reduce public confidence in the safe use of acetaminophen for fever and pain, likely resulting in an increased rate of consumers consulting physicians for treating minor self-limiting conditions [48].

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SECTION 7 ATTACHMENT

ATTACHMENT 1: PUBLISHED CLINICAL STUDIES OF ACETAMINOPHEN PACKAGE SIZE RESTRICTIONS

Summary of Published Clinical Studies of Acetaminophen Package Size Restrictions

Citation Country	Study Time Period	Study Objective	Study Design	Outcomes	Conclusion
Prince MI, et al. Lancet 2000;355: 2047-8. UK[a]	10/95-12/99	Examine referrals to a tertiary liver unit and national liver transplantation requests before and after September 1998	• Retrospective • Examined referrals to a tertiary liver unit (Freeman Liver Unit, Newcastle-upon-Tyne, UK) for number and severity with APAP hepatotoxicity • Examined national liver transplantation requests due to APAP toxicity based on data from the UK Transplant Special Support Authority (UKTSSA)	• Median monthly referral rate to the tertiary liver unit fell from 2.5 to 1 after restrictions ($p<0.02$). Annual rate of referrals was falling in the three years before September 1998 by an average of 4.5 patients per year and fell by 10 patients per year after restrictions were introduced • Nationally, median monthly number of referrals for transplants fell from 3.5 to 2 after restrictions ($p<0.02$). The number of referrals had been increasing yearly in the 3 years prior to September 1998 • Median dose of APAP for patients admitted to Freeman was 35 g before September 1998 and 25 g after • Overdose severity of referred patients remained constant throughout study	Substantial reductions in the frequency of severe APAP hepatotoxicity locally and nationally after restrictions

Summary of Published Clinical Studies of Acetaminophen Package Size Restrictions

Citation Country	Study Time Period	Study Objective	Study Design	Outcomes	Conclusion
Turvill JL, et al. Lancet 2000 355:2048-9. UK[a]	9/95-8/99	Assess whether the introduction of blister packs had an impact on the occurrence and severity of APAP overdose in the UK	• Retrospective • Examined all APAP overdoses presenting to the Royal Free Hospital in London, England • Used the occurrence of benzodiazepine overdose as a control	• For the three years preceding the APAP restrictions, the yearly occurrence of APAP overdoses was consistent • In the year following APAP restrictions, there was a 21% overall reduction in APAP overdoses and a 64% reduction in severe APAP overdoses (defined as overdoses in which antidote therapy was indicated to prevent acute liver injury). During this period benzodiazepine overdoses remained stable	Study suggests a significant change in overdose behavior after introduction of APAP blister packs

Summary of Published Clinical Studies of Acetaminophen Package Size Restrictions

Citation Country	Study Time Period	Study Objective	Study Design	Outcomes	Conclusion
Hawton K, et al. BMJ 2001;322: 1-7. UK[a]	9/96-9/99	To evaluate the effects on suicidal behavior of legislation limiting the size of packs of APAP and salicylates sold over-the-counter	• Prospective, before and after • Examined Office for National Statistics data from England and Wales on drug related deaths and deaths from undetermined causes and extracted data on deaths of people ≥12 years where only APAP or salicylates were involved for 9/96-9/99 • Examined data from five liver units in England for number of admissions after APAP overdose, patients listed for liver transplantation, and patients receiving liver transplants for 10/96-9/99 • Examined data from seven hospitals (Oxford, Manchester, Bristol and Bath) for self-poisonings with APAP and salicylate products for 9/97-9/99 • Examined monthly sales data of APAP and salicylate preparations from Intercontinental Medical Statistics data for 9/96-9/99	• After restrictions, a significant 21% decrease in the number of deaths attributable to APAP alone (p=0.01) and 48% decrease for salicylates alone (p=0.02), but no significant difference in numbers of deaths due to combinations with APAP and/or salicylates • After restrictions, the number of patients with hepatic APAP poisoning admitted to liver units declined by 30%, the total number of listings for liver transplantations more than halved, and 66% fewer patients underwent liver transplantation due to APAP poisoning • After restrictions, the proportion of non-fatal overdose cases involving APAP of any kind did not change, but the absolute number declined significantly (p<0.001) by 11% • After restrictions, the proportion of non-fatal overdoses involving APAP compounds significantly (p=0.001) increased and the proportion of non-fatal overdoses involving APAP alone significantly decreased (p=0.001) • The mean number of APAP tablets taken in non-fatal overdoses after restrictions decreased by 7% and the proportions involving more than 32 tablets decreased significantly (p=0.01) by 17%; there was no change in the number of salicylate tablets	Legislation restricting pack sizes of APAP and salicylates in the UK has had substantial beneficial effects on morbidity and mortality associated with self-poisoning with these drugs

Summary of Published Clinical Studies of Acetaminophen Package Size Restrictions

Citation Country	Study Time Period	Study Objective	Study Design	Outcomes	Conclusion
Hawton K, et al. BMJ 2001;322: 1-7. (cont.) UK[a]				• While there was a significant decrease in the mean number of APAP tablets sold per pack there was also a significant increase in the number of packs sold such that the total number of tablets sold did not significantly change • After restrictions, there was no significant change in the mean highest blood APAP concentration, but the mean highest prothrombin times decreased slightly	

Summary of Published Clinical Studies of Acetaminophen Package Size Restrictions

Citation Country	Study Time Period	Study Objective	Study Design	Outcomes	Conclusion
Thomas MR, et al. BMJ 2001;322: 553. UK[a]	2/98-8/98 and 2/99-8/99	Examine the effect of APAP sales restrictions on all cases of self poisoning	• Surveyed all admissions at a general hospital in Pembrokeshire for overdose before (February-August 1998) and after (February-August 1999) APAP sales restrictions	• 116 patients were admitted for any overdose in 1998 and 112 patients were admitted in 1999 • 52 (45%) APAP poisonings occurred in 1998 and 40 (36%) in 1999 • 68% of patients took more than 16 APAP tablets in 1998 and 51% took more than 16 APAP tablets in 1999 • Non-APAP poisonings increased from 64 cases in 1998 to 72 cases in 1999 • Average time that patients spent in the hospital was the same during both periods (2.6 days)	Patients are switching to alternative agents for self poisoning

Summary of Published Clinical Studies of Acetaminophen Package Size Restrictions

Citation Country	Study Time Period	Study Objective	Study Design	Outcomes	Conclusion
Hughes B, et al. J Clin Pharm Ther 2003;28: 307-10. UK[a]	4/95-1/02	Investigate the local impact of 1998 UK legislation	• Retrospective • Examined data on number of patients admitted to University Hospitals, Birmingham NHS Trust due to APAP overdose and number admitted to the Queen Elizabeth Hospital liver unit with APAP-induced hepatotoxicity	• Prior to the restrictions, an average of 360 people per year were admitted for APAP overdose compared to 250 people per year after the restrictions • Prior to the restrictions, an average of 76 people per year were admitted to the liver unit for APAP overdose compared to an average of 38 people per year after the restrictions	Pack size restrictions of APAP may have effectively reduced the incidence and severity of poisoning. However, there are also other explanations for observations (ie, ready availability of acetylcysteine, publication and use of standard protocol for treating APAP poisonings)

Summary of Published Clinical Studies of Acetaminophen Package Size Restrictions

Citation Country	Study Time Period	Study Objective	Study Design	Outcomes	Conclusion
Hawton K, et al. BMJ 2004; 329:1076-9. UK[a]	1993-2002	Assess the longer term effect of APAP restriction and investigate possible substitution of overdose method with the non-steroidal anti-inflammatory drug ibuprofen, which was not included in the legislation	• Before and after study • Examined data supplied by Office for National Statistics for England and Wales on drug related deaths on people 12 years and older due to APAP, salicylates, and ibuprofen between 1993 and 2001 • Examined data from liver units in England and Scotland on number of patients admitted after APAP overdose, listed for liver transplantation, and undergoing liver transplantation between 1996 and 2002 • Examined data from five general hospitals in Oxford, Manchester, and Derby for presentations for self-poisoning with APAP, salicylates, ibuprofen, and other drugs between 1997 and 2001 • Examined sales of analgesics using data from Intercontinental Medical Statistics	• Compared with the two years before restrictions, significant ($p \leq 0.02$) decreases in the number of deaths related to APAP (-29%) and salicylates alone (-46%) in the year after restriction were observed and sustained for the subsequent two years. Findings were similar for APAP and salicylates taken with other drugs • There were few deaths involving ibuprofen both before and after the restrictions • The mean annual admissions to a liver unit for APAP poisoning decreased from 349 in the two years before restrictions to 230 in the four years after, listings for liver transplantation decreased from 43 to 30, and the number of transplants decreased from 32 to 21.5 • For non-fatal self poisonings, there was a 15% reduction with APAP in the year after restriction but no reduction in subsequent years, no significant change with salicylates after restriction, and an increase of 27% with ibuprofen in the second and third years after restrictions • The number of tablets taken in APAP and salicylate non-fatal overdoses significantly ($p \leq 0.02$) decreased in the three years after restrictions • APAP non-fatal overdoses of more than 32 tablets decreased significantly ($p \leq 0.02$) in the first year and the subsequent two years after restrictions	Legislation restricting pack sizes of analgesics in the UK has been beneficial

Summary of Published Clinical Studies of Acetaminophen Package Size Restrictions

Citation Country	Study Time Period	Study Objective	Study Design	Outcomes	Conclusion
Hawton K, et al. BMJ 2004; 329:1076-9. (cont.) UK[a]				• 520 million APAP tablets sold in 1996-7 and 580 million sold in 2001-2 • Sales of aspirin tablets halved during study period	

Summary of Published Clinical Studies of Acetaminophen Package Size Restrictions

Citation Country	Study Time Period	Study Objective	Study Design	Outcomes	Conclusion
Morgan O, et al. J Pub Health 2005;27 (1):19-24. UK[a]	1993-2002	Evaluate the impact of 1998 APAP sales restrictions, four years after implementation, on mortality and hospital activity	• Retrospective • Analysis of APAP related deaths from 1993-2002 based on mortality data provided by the Office for National Statistics for England and Wales • Analysis of hospital admissions with a primary diagnosis of APAP poisoning based on data provided by the Department of Health between 1995/1996 and 2001/2002	• Mortality rates from APAP only were about 4.5 per million in 1997, 2.8 per million in 1999, 3.1 per million in 2001, and 2.2 per million in 2002 • Almost half of APAP-related deaths were due to intentional self-poisoning • Deaths from compound APAP remained relatively constant over study period • There was a decreasing overall trend in mortality rates for APAP only and for other drug poisonings, excluding opioids and drugs of misuse • Hospital admissions due to APAP poisonings were about 27,000 in 1995/1996, 33,000 in 1997/1998, and 25,000 in 2001/2002.	Between 1993 and 2002, mortality rates and hospital admissions due to APAP poisoning declined. This followed overall trends for other drug poisoning, excluding opioids and drugs of misuse

Summary of Published Clinical Studies of Acetaminophen Package Size Restrictions

Citation Country	Study Time Period	Study Objective	Study Design	Outcomes	Conclusion
Hawkins LC, et al. Clin Toxicol 2006; 44(5):657-8. UK[a]	1996-2004	Determine the success of the restriction legislation by measuring the number of tablets taken per overdose	• Retrospective • Data on APAP overdoses was extracted from the Guy's and St. Thomas' poison center database and restricted to intentional self-harm events involving patients older than 12 years	• Poison centers received >90,000 inquiries about APAP overdoses during study period • Proportion of cases where 16 tablets were taken increased post-1998 (nearly 50% of all cases between 1999-2004) • Proportion of cases where 17-32 and 33-100 tablets were taken declined post-1998 • Proportion of cases where >100 tablets were taken remained constant over study period (<5% of cases) • Median number of tablets taken pre-1988 was 25 in males and 20 in females and post-1998 was 21 in males and 16 in females • Variables were constant between 1999 and 2004	Study suggests that the legislation has been associated with a reduction in the number of tablets taken in APAP overdose

Summary of Published Clinical Studies of Acetaminophen Package Size Restrictions

Citation Country	Study Time Period	Study Objective	Study Design	Outcomes	Conclusion
Greene SL, et al. Postgrad Med J 2006;82: 520-3. UK[a]	2001-2004	To determine the degree of adherence to legislation introduced in 1998 restricting the availability of over-the-counter APAP	• Prospective, observational study • Examined source of APAP ingested in patients presenting with acute overdose of APAP to an emergency department in an inner city London teaching hospital from 11/01-3/03 • Examined ability to purchase APAP in a manner contravening the 1998 legislation (64 APAP 500 mg tablets) from 24 different stores (pharmacy and nonpharmacy outlets) in south London in 2004	• 107 patients presented to the emergency department with an acute overdose of APAP • 77 patients reported ingesting more than 16 APAP 500 mg tablets • 35 patients who ingested more than 16 APAP 500 mg tablets purchased the APAP for the purpose of an overdose (16 of these patients obtained the tablets in a manner contravening the 1998 legislation and 15 of these patients purchased the APAP from multiple different stores) • 38 patients who ingested more than 16 APAP 500 mg tablets had the tablets already stored at home • In 70% of the stores visited, the investigators were able to purchase more than the restricted amount of APAP (four of eight pharmacies, four of six supermarkets, and nine of ten corner stores, newsagents, and petrol shops)	Legislation limiting the availability of over the counter APAP is not being adhered to in south London. A significant number of patients ingesting a potentially toxic dose of APAP report purchasing the tablets in a manner contravening the legislation.

Summary of Published Clinical Studies of Acetaminophen Package Size Restrictions

Citation Country	Study Time Period	Study Objective	Study Design	Outcomes	Conclusion
Morgan OW, et al. PLoS Med 2007; 4 (4):e105. UK[a]	1993 - 2004	To evaluate if the recent fall in the number of APAP deaths is different to trends in fatal poisoning involving aspirin, APAP compounds, antidepressants, or nondrug poisoning suicides because of package size restrictions	• Retrospective • Interrupted time-series analysis • Analysis of drug-poisoning deaths from 1993 – 2004 based on mortality data provided by the Office for National Statistics for England and Wales	• Approximately 2,200 deaths involving APAP occurred from 1993 - 2004 • The age standardized mortality rate increased from 8.1 per million in 1993 to 8.8 per million in 1997, subsequently falling to 5.3 per million in 2004 • After regulations were introduced, deaths dropped by 2.69 per million • Antidepressants, aspirin, and APAP compounds demonstrated a similar increase until 1997 followed by a decrease after restrictions in age standardized mortality rate • Nondrug poisoning suicide also declined from 1993 - 2004	The observed decline in APAP mortality may not be due to package size restriction, but rather a wider trend in the reduction of drug-poisoning suicide