Recommendations for FDA Interventions to Decrease the Occurrence of Acetaminophen Hepatotoxicity

Prepared for Janet Woodcock, M.D.
Acting Director, Center for Drug Evaluation and Research

By

The Acetaminophen Hepatotoxicity Working Group
Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health and Human Services

February 26, 2008

This report represents the recommendations of a working group asked by former CDER Director Dr. Steven Galson to consider FDA interventions that could decrease the number of cases of unintentional and intentional overdose leading to liver injury from over-the-counter and prescription drug products. CDER recognizes that acetaminophen-related hepatotoxicity is a significant public health problem. The working group used reviews completed by the Office of Surveillance and Epidemiology (OSE), the Office of Nonprescription Products (ONP) and the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) as a basis for discussion, as well as other material submitted to FDA in other contexts (e.g., citizen petitions, responses to proposed rulemaking).

Outline of Report

EXECUTIVE SUMMARY OF CDER WORKING GROUP RECOMMENDATIONS

The recommendations of the working group are described below and discussed in greater detail in Section II. The report (Section III) concludes by providing an estimate of the impact of each intervention and summarizing the steps that FDA can take within the next 3-6 months to implement the recommendations. The table in Appendix A of the report summarizes the recommendations and their implementation.

To reduce unintentional overdose with over-the-counter (OTC) acetaminophen products:

1. Enhance public education efforts (also may reduce intentional overdoses)
   - Develop concise, clear messages
   - Increase partnerships with other governmental agencies, health professionals, industry, consumers, and media
   - Improve FDA's own educational efforts
2. Improve labeling (may also reduce intentional overdoses in suicide gesture[1]):
   - Prominently display the name acetaminophen on principal display panel
   - Highlight/bold acetaminophen in active ingredient list
   - Include warning that taking more than recommended amount may cause severe liver injury
   - Include warning that product should not be used with other products containing acetaminophen
   - Include warning about need for prompt medical attention after acetaminophen overdose even when no symptoms of a health problem are present
   - Include warnings for people with liver disease
   - Include warnings for alcohol users (severe liver damage may occur if you take 3 or more alcoholic drinks every day while using the product) and include a statement that they should use less than the maximum daily dose unless a specific dose is recommended
   - Require prominent warnings about liver toxicity on immediate containers
3. Limit the maximum adult daily dose to an amount no greater than 3250 mg, except there should be a lower daily maximum for patients taking 3 or more alcoholic drinks every day while using acetaminophen products
4. Limit the tablet strength for immediate-release formulations to a maximum of 325 mg and the single adult dose to a maximum of 650 mg (also may reduce intentional overdose). Limit tablet strength for extended-release formulations commensurate with total daily dose and the dosing increment
5. Limit options in pediatric liquid formulations
   - Limit pediatric liquid formulation to one mid-strength concentration (compared to multiple dose strengths available now)
   - Require that a measuring device (e.g., calibrated cup with dosing increments representative of the units of measure in the labeling) be included in each package
   - Include dosing instructions for children under 2 years if accurate dosing instructions can be determined and adequate efficacy data exist to support dosing
6. Eliminate combination products
7. Identify further research needs (may also reduce intentional overdoses)

To reduce unintentional overdose with prescription (Rx) combination products:

1. Enhance public education efforts (see OTC products above)
2. Improve labeling

[1] If an attempted suicide involves a suicidal action unlikely to have any potential of being fatal, it is called a suicide gesture, From Merck Manual Online, retrieved 2/25/08 from http://www.merck.com/mmhe/sec07/ch102/ch102a html

- Require warning on container given to patients by pharmacist that provides message consistent with OTC warnings and prominently display acetaminophen as an active ingredient on the container
- Include Medication Guide with information about hepatotoxicity similar to OTC labeling
- Include a boxed warning with information similar to OTC labeling

3. Require unit-of-use packaging (defined as packaging by the manufacturer for direct distribution to the patient by the pharmacist; can include blister packages and pre-packaged containers)
4. Limit maximum adult daily dose similar to OTC maximum daily dose
5. Limit the tablet strength of immediate-release formulations to maximum of 325 mg and the single adult dose to 650 mg (also may reduce intentional overdoses by lowering the total exposure for the same number of pills ingested). Extended-release formulations should be similarly permitted, with tablet strength determined by dosing interval and total daily dose
6. Identify further research needs

Section III of the report provides recommendations for follow-up and implementation.

I. INTRODUCTION: THE SCOPE OF THE PROBLEM

Acetaminophen (also abbreviated as APAP on prescription containers dispensed by pharmacists; some countries outside the United States refer to it as paracetamol) is one of the most commonly used drugs in the United States to reduce pain and fever.[2] An important reason for its popularity is that it lacks the gastrointestinal toxicity of the nonsteroidal antinflammatory drugs (NSAIDs). Despite its undeniable popularity, efficacy, and general safety when used according to dosing instructions, acetaminophen can also cause hepatotoxicity, usually when the consumer exceeds the recommended dosage. There are, however, instances where hepatotoxicity is reported with dosing at the total daily recommended dose. Acetaminophen hepatotoxicity can range from abnormalities in liver function blood tests to acute liver failure and death.

Beginning in the late 1990s, research emerged indicating that acetaminophen hepatotoxicity was a major cause of acute liver failure (ALF) in the United States; approximately 40% of the cases were related to unintentional overdose leading to liver injury.[3] Responding to these concerns, FDA took numerous steps to reduce acetaminophen hepatotoxicity. These initiatives included convening an Advisory Committee meeting in 2002, engaging in a public education campaign in early 2004, and issuing proposed regulations about over-the-counter (OTC) labeling for acetaminophen products in December of 2006 (see Appendix B for a more detailed timeline; see Appendix C for the proposed OTC regulations).[4]

Despite these efforts, recent studies indicate that unintentional and intentional overdoses leading to severe hepatotoxicity continue to occur. In a study published by the Acute Liver Failure Study Group (ALFSG) in 2005 of ALF at 22 tertiary care centers in the United States, the proportion of ALF cases related to acetaminophen rose from 28% in 1998 to 51% in 2003.[5] Acetaminophen-related hepatotoxicity was the leading cause of ALF in the United States, with 48% of the cases being unintentional overdose during this period. The high percentage of cases of liver failure related to unintentional acetaminophen overdose was reaffirmed in a population based study published in 2007.[6] Serious adverse event reports related to hepatobiliary injury are still reported to FDA with significant frequency.[7] Summarizing data from 6 different surveillance systems, from 1990 - 2001 there were 56,000 emergency room visits, 26,000 hospitalizations, and 458 deaths annually from acetaminophen overdose.[8] Acetaminophen has a narrow

---

[2] Between 2001 and 2005, 24 – 29 billion doses of acetaminophen (in all forms) were sold. OTC accounted for 60 – 68% of the sales by number of doses. One-half of the OTC sales were for combination products. For prescription products, approximately 160 – 180 million prescriptions of acetaminophen products are written per year. From Laura Governale review in appendix H. Acetaminophen was the most commonly used prescription and over-the-counter drug used in a 1-week prevalence survey conducted from Feb. 1998 – Dec. 1999. From Kaufman DW, et. al. JAMA. 2002;287(3): 337-44

[3] Schiødt FV, Rochling FA, Casey DL, Lee WM. Acetaminophen toxicity in an urban county hospital. N Engl J Med. 1997 Oct 16;337(16):1112-7.

[4] Internal Analgesic, Antipyretic, and Anitirheumatic Drug Products for Over-the-Counter Human Use: Proposed Amendment of the Tentative Final Monograph: Required Warnings and Other Labeling, 71 FR 77314-52 (December 26, 2006)(Docket No. 1977N-0094L) (amending 21 CFR 201.66, 201.322, 201.325, 343.50) [hereinafter Proposed OTC Regulations].

[5] It should be noted that some of this increase may be related to a change in the parameters to identify acetaminophen associated events. Larson AM, Polson J, Fontana RJ, Davern TJ, Lalani E, Lee WM et al. Acute Liver Failure Study Group (ALFSG). Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. Hepatology. 2005 Dec;42(6):1364-72.

[6] William A. Bower, M.D., Matthew Johns, M.P.H., Harold S. Margolis, M.D., Ian T. Williams, Ph.D.,and Beth P. Bell, M.D. Population-Based Surveillance for Acute Liver Failure . Am J Gastroenterol 2007;102:2459–2463.

[7] On 10-24-07, a report was run in AERS DataMart that looked at the number of serious adverse event reports characterized as 5, 10 and 15 day expedited reports. Acetaminophen was the primary drug and all hepatobiliary terms were searched between 1-1-05 and 9-30-07. There were 395 reports. Hepatic failure is the most common reported event (207/395).

[8] Nourjah P, Ahmad SR, Karwoski C, Willy M. Estimates of Acetaminophen (Paracetamol)-associated overdoses in the United States. Pharmacoepidemiol Drug Saf. 2006 Jun; 15(6): 398-405.

therapeutic margin, that is, there is little difference between the current maximum recommended dose of acetaminophen and the doses that are associated with a potentially elevated risk of hepatotoxicity.[9]

Recognizing the continued occurrence of acetaminophen hepatotoxicity as a significant public health problem, Dr. Steven Galson, former CDER Director, charged a working group within CDER to recommend FDA interventions that would decrease the number of cases of acetaminophen induced liver injury (see Appendix D for list of working group members). The working group met and discussed various interventions, using numerous sources to inform its discussion. These sources include internal reviews and recommendations completed by OSE, ONP and DAARP.[10] These reviews (attached as Appendices E, F, and G) provide a more detailed history and analysis of various interventions under consideration. The working group also consulted other material focusing on acetaminophen and liver toxicity that had been submitted to FDA in other contexts.[11] The working group discussed the interventions and attempted to reach a consensus on each.

The ability of acetaminophen to cause liver toxicity when it is improperly used is not a reason to discourage its proper use. Compared to alternative pain medications, principally narcotics and NSAIDS, it is relatively safe when used correctly and provides an important option compared to other pain medications. We would not want FDA interventions to address the hepatotoxicity risk of acetaminophen to be misinterpreted as an agency position that NSAIDs are safer than acetaminophen. The working group recognizes that NSAIDS, especially with long-term use, result in important gastrointestinal and renal morbidities. The purpose of the interventions is to reduce acetaminophen-related hepatotoxicity, not to decrease appropriate acetaminophen use or to drive people to use NSAIDs instead.

Realistically, it will be difficult to completely eliminate all cases of hepatotoxicity because we know patients will not always take drugs appropriately and according to directions and because some individuals may be unusually sensitive to liver injury. It is important, however, to initiate measures that could to the extent possible decrease the number of unintentional overdose cases. There is no single factor that leads consumers (also referred to as patients in this report) to develop acetaminophen-related liver injury. The contributing conditions for these cases are multi-factorial and require different interventions that attempt to address each factor. For example, when someone takes an amount greater than labeled, it is unclear whether it is a case of failing to read the directions, failing to understand the directions, failing to understand that severe liver injury can result from not following the directions or failing to realize that more than one of the medications used contained acetaminophen. Thus, it is necessary to address all of these causes in attempting to prevent future cases, making clear directions conspicuous and easy to understand and making consequences of overdose unequivocally clear. We can

[9] Based on liver injury being reported in people with doses that are slightly above 4 grams per day in the FDA Adverse Event Reporting system data and in the ALFSG report of 2005.

[10] Office of Surveillance and Epidemiology, *OSE Safety Review (Acetaminophen, Hepatotoxicity, Death)*(February 5, 2007)[hereinafter OSE Report]; Office of Nonprescription Products, *Acetaminophen-Induced Hepatotoxicity* (March 8, 2007) [hereinafter ONP Report]; Division of Anesthesia, Analgesia, and Rheumatology Products, *Assessment of the Analgesic Efficacy and Hepatotoxicity of Opioid/Acetaminophen Combination Products* (March 12, 2007) [hereinafter DAARP Report].

[11] Pharmacists Planning Service, Inc. (PPS), http://www.ppsinc.org (filed citizen petition dated September 23, 2006, docket number 2006P-0423); FDA Type C Meeting with McNeil Consumer Healthcare, *Educational Initiatives on Over-the-Counter Medicines*, April 18, 2007; Comments to Proposed OTC Regulations; Buc & Beardsley (on behalf of McNeil Consumer & Specialty Products), *Complaint and Request for Correction Pursuant to the Federal Data Quality Act Concerning "Consumer Campaign on Safe Use of OTC Pain Products"* (May 18, 2004), From *HHS Information Quality Web Site: Information Requests for Corrections and HHS' Res*ponses website, retrieved February 25, 2008, from http://www.aspe hhs.gov/infoquality/requests.shtml (Request for Reconsideration, October 22, 2004, also available on the cite).

speculate on the factors that may contribute to unintentional overdose based on information reported in the literature.[12]

1. Consumers perceive that OTC products are extremely safe and not likely to lead to serious toxicity. The marketing of OTC products emphasizes their safety and this perception may be reinforced by the availability of package sizes with large numbers of pills.
2. Consumers do not read the labels or follow the directions for use on OTC and prescription products.
3. Some of the prescription products are not adequately labeled to identify acetaminophen as an ingredient. Acetaminophen is often labeled as APAP on the prescription containers.
4. Consumers are not aware that acetaminophen can cause serious liver injury, in part because product labels do not adequately warn of this problem.
5. Consumers are not aware that acetaminophen is present in many OTC and prescription products and are not aware that they are exceeding the maximum daily dose.
6. Some populations (e.g., certain alcohol users and people with liver disease) may be more susceptible to hepatic injury.
7. The symptoms of acetaminophen overdose may not appear for up to three days, so people may continue to take acetaminophen and increase the damage. The symptoms of liver injury may mimic the condition that they are treating (e.g., flu symptoms).
8. Because patients may not get adequate pain relief after taking the recommended dosage of acetaminophen, they may take more than the recommended amount or use other products that also contain acetaminophen. This behavior may reflect the lack of knowledge that acetaminophen can be toxic to the liver or that the other products also contain acetaminophen.
9. Patients develop tolerance to narcotics and need to increase the dose of prescription combination products. If they do this on their own, they may not realize that they are increasing the dose of acetaminophen to toxic levels.
10. Combination narcotic products are commonly used because of limited non-narcotic options and greater restrictions on availability for higher scheduled single-ingredient narcotic analgesics.

The working group was also impressed with the fact that current dosing recommendations and tablet sizes of acetaminophen leave little room for error. The 4 gram per day recommended dose is also the maximum safe dose, one that must not be exceeded, an unusual situation for any drug, particularly an OTC drug, one placing a large fraction of users close to a toxic dose in the ordinary course of use.

[12] Stumpf JL, Skyles AJ, Alaniz C, Erickson SR. Knowledge of appropriate acetaminophen doses and potential toxicities in an adult clinic population. J Am Pharm Assoc (2003). 2007 Jan-Feb;47(1):35-41. Chen L, Schneider S, Wax P. Knowledge about acetaminophen toxicity among emergency department visitors. Vet Human Toxicology. 2002; 44: 370-373. Li SF, Lacjer B, Crain EF. Acetaminophen and ibuprofen dosing by parents. Pediatr Emerg Care 2000; 16:394-7.

II. **WORKING GROUP RECOMMENDATIONS**

The recommendations focus on *unintentional*[13] (rather than *intentional*[14]) acetaminophen overdoses because unintentional overdoses appear to be more likely to be influenced by interventions. The working group believes it will be difficult to decrease liver injury in cases of intentional overdoses by people intent on harming themselves. The working group discussed interventions in the United Kingdom (principally the sales restriction and limits on the number of tablets in a package) that appear to have decreased the severity of overdose with acetaminophen.[15] The working group opted not to recommend similar interventions because it is difficult to separate the effect related to the sales restriction from the package size limit. Under our current regulations sales restriction is not an option and would make it difficult for people to purchase acetaminophen for appropriate chronic use (see Section II.A.8.2 for discussion). Such interventions may be effective, however, for people taking overdoses as gestures without really intending to hurt themselves. Because hepatotoxicity due to intentional overdose continues to be a serious health problem,[16] when an intervention addresses intentional in addition to unintentional overdoses, the report notes that fact.

The report first discusses recommended interventions for OTC acetaminophen products and then discusses interventions involving prescription products. For each recommendation, the report describes the recommendation, sets forth the supporting rationale, provides suggested mechanisms[17] to implement the recommendation with an estimated deadline for completion, and concludes with potential challenges to implementing the recommendation. The interventions that the working group considered but rejected are summarized after the recommended interventions at the end of the OTC and prescription products sections.

There are several implementation challenges that apply to almost all recommendations; the report, therefore, does not reiterate them for each recommendation. These overarching challenges include:

1. Timely implementation of the recommendations will require substantial resources and will require the collaborative efforts of several offices within CDER and the Office of the Commissioner.
2. It will be important to understand whether the interventions are successful. Several databases must be identified that will accurately assess whether the number of cases of hepatotoxicity is declining over time. The acute liver failure data from the ALFSG can be one source but there should also be a database that captures injury less severe than liver failure. The success of the intervention needs to be reassessed at pre-defined interval. The intervals will depend on what is implemented and the estimated time needed to show an effect.

---

[13] *Unintentional* refers to the ingestion of more than the label recommends for a therapeutic purpose not to cause injury. The term also includes individuals who have an underlying risk factor that may predispose them to liver injury even at the current labeled dose**.**

[14] *Intentional* overdose refers to intentionally taking excessive amounts of acetaminophen to cause harm, usually as a single dose (e.g., attempted suicide).

[15] Hawkins LC, Edwards JN, Dargan PI. Impact of restricting paracetamol pack sizes on paracetamol poisoning in the United Kingdom: a review of the literature. Drug Saf 2007; 30: 465-79.

[16] From pp. 21-23 OSE review, adverse event reports with acetaminophen associated with self-injurious behavior reports and suicide have increased significantly since about 1998, and have continued to increase in the latest tabulation from 2005; between 2002 and 2005, death from suicide associated with acetaminophen have increased from about 200 to about 600 annually; of the 2,407 domestic reports related to ingestion of acetaminophen in suicidal and self-injurious behavior in the AERS database (since inception, 86% (2,080) had a death outcome. From Nourjah P, Ahmad SR, Karwoski C, Willy M. Estimates of Acetaminophen (Paracetamol)-associated overdoses in the United States. Pharmacoepidemiol Drug Saf. 2006 Jun; 15(6): 398-405. Depending on the data source, 42-74% of overdoses were intentional.

[17] The mechanisms the working group considered are: statutory changes, regulatory changes (with notice and comment rulemaking process), NDA/ANDA supplement process, guidances, Advisory Committee meetings, other public hearings/meetings, citizen petition responses, public education mechanisms summarized in the public education recommendation, voluntary or mandatory market withdrawals.

3. Once decisions are made about interventions, implementation should proceed expeditiously. If rulemaking is necessary (rules typically take years to complete), the documents should be identified as high priorities and the clearance process streamlined.
4. Legal hurdles should be identified early and vetted by OCC expeditiously.
5. The problem is multi-factorial and will not be solved without involvement of patients, manufacturers, health care providers, professional associations, the media, retailers and government agencies in addition to FDA.

A. Over-the-Counter (OTC) Product Recommendations

OTC acetaminophen products are one of the primary causes of hepatotoxicity. The working group recommends the following types of interventions to reduce hepatotoxicity from OTC acetaminophen products: (1) education, (2) enhanced labeling, (3) a change in the maximum adult daily dose, (4) a change in tablet strength and recommended single adult dose, (5) a change in the permitted liquid formulations, (6) elimination of OTC combination products, and (7) additional research. All the acetaminophen OTC products except for two products are marketed under the monograph and changes in the monograph will require notice and comment rulemaking. The two OTC products marketed under NDAs are an extended-release adult formulation and rectal suppositories for children. Any changes to these applications will be made by amending the NDA.

1. Enhance Public Education Efforts

Working Group Recommendations: Increase FDA efforts (with increased funding) to educate consumers and health care professionals about acetaminophen hepatotoxicity by:

(1) developing concise, clear messages;

(2) pursuing partnerships with:
- **other government agencies (e.g., CDC, NIH, AHRQ, FTC, [18] DEA, state pharmacy boards[19])**
- **prescribing health professionals**
- **pharmacists**
- **professional and disease organizations (e.g., gastrointestinal and liver-related)**
- **manufacturers (brand-name and generic) and retailers**
- **patient groups**
- **the media; and**

(3) improving FDA's own educational efforts by:
- **Improving access to information for consumers and health providers by:**
  - **creating/updating a central page about acetaminophen and liver toxicity[20]**
  - **modifying FDA's search engines so that people searching for side effects of pain relievers, Tylenol, acetaminophen, APAP, or liver injury get directed to FDA's central acetaminophen page**
  - **developing free continuing medical education course on-line for physicians, nurses, pharmacists, and other health professionals**
  - **publishing in the medical literature on hepatotoxicity**

[18] The FTC partnership focuses on ensuring that OTC advertising is not misleading.

[19] For possible further pharmacy-related outreach, see Steven Galson, "Letter to State Boards of Pharmacy, Acetaminophen Hepatotoxicity and Nonsteroidal Anti-inflammatory Drug (NSAID)-related Gastrointestinal and Renal Toxicity," January 22, 2004, available on FDA's website at http://www fda.gov/cder/drug/analgesics/letter htm; National Association of Boards of Pharmacy. http://www.nabp net/; American Pharmacists Association (APhA), http://www.pharmacist.com (submitted comments on December 2006 proposed OTC rule-making (docket No. 1977N-0094L); Pharmacists Planning Service, Inc. (PPS), http://www.ppsinc.org (filed citizen petition dated September 23, 2006, docket number 2006P-0423).

[20] http://www.fda.gov/cder/drug/analgesics/default htm.

    - **seeking to modify popular non-FDA medical consumer web pages (e.g., wikipedia, WebMd)**
- **Publishing articles about the issue both in the FDA *Consumer* and on the new consumer webpage[21]**
- **Using various public education tools (e.g., labeling, Public Health Advisories,[22] documents described in Guidance *Drug Safety Information—FDA's Communication to the Public* [23] and on FDA's Web Site,[24] Guidance *Useful Written Consumer Medication Information (CMI)*)[25]**
- **Funding studies about consumer awareness of acetaminophen and liver toxicity, as well as the most effective public education tools**

Rationale: There is extensive evidence that hepatotoxicity caused by acetaminophen use may result from lack of consumer awareness that acetaminophen can cause severe liver injury.[26] People may take more than the recommended dose of OTC pain relievers because they think that taking more acetaminophen will more effectively control pain than with the recommended dose and that taking more than the recommended dose does not pose any serious health hazards. Consumers also may not be aware that signs and symptoms of acetaminophen overdose may not appear for up to three days, so people may continue to take acetaminophen and increase the damage.

Consumers may not be aware that acetaminophen is present in many OTC combination products, so they may unknowingly exceed the recommended acetaminophen dose if they take more than one acetaminophen product without knowing that both contain acetaminophen.[27] Acetaminophen may be a difficult name to remember and recognize even if drug products are appropriately labeled, which can also add to consumer confusion and inadvertent overdose. Organizations representing health professionals, diseases, patients, and industry all support enhanced educational efforts.[28] Such support is crucial since the problem is multi-factorial and most likely will not be solved without involvement of the various stakeholders.

Mechanisms to Implement and Suggested Timeline: Many of the components in this recommendation could be implemented immediately. Within the next 3-6 months, CDER should develop new educational tools and begin to implement them. To accomplish this goal, staff from OSE and OND should be identified to work with CDER's Office of Training and Communication and the Office of the Commissioner to identify the best mechanisms for enhancing public education and to conduct appropriate outreach to FDA partners described above.

---

[21] http://www.fda.gov/consumer/.

[22] *Public Health Advisories*, retrieved February 25, 2008, from http://www fda.gov/cder/news/pubpress htm (no public health advisories with titles listing acetaminophen, aspirin, ibuprofen or naproxen, but includes public health advisory dated December 23, 2004 entitled *Non-Steroidal Anti-Inflammatory Drug Products (NSAIDS)*(December 23, 2004))

[23] Retrieved February 25, 2008, from http://www fda.gov/cder/guidance/7477fnl htm (March 2007).

[24] *Index to Drug-Specific Information*, retrieved February 25, 2008, from http://www fda.gov/cder/drug/DrugSafety/DrugIndex.htm (as of August 2, 2007, aspirin, ibuprofen, and naproxen were included in this list, but acetaminophen was not listed).

[25] Retrieved February 25, 2008, from http://www fda.gov/cder/guidance/7139fnl htm (July 26, 2006).

[26] ONP review pp. 26-28 (Shaoul et al. 2004 and Lagerlov et al. 2003).

[27] The McNeil Habits and Practices Survey provide relevant data. This survey demonstrates that consumers did not know or could not recall what certain prescription products contained. Only one of 61 consumers who were taking Vicodin, Percocet, or Endocet knew that the product contained acetaminophen. None knew what the other active ingredient was in any of these products. Retrieved February 25, 2008, from http://www fda.gov/ohrms/dockets/ac/02/briefing/3882B1_13_McNeil-Acetaminophen htm

[28] American Liver Foundation, American Association for the Study of Liver Diseases, McNeil Consumer Healthcare.

Challenges to Implementation:

- The FDA's 2004 educational campaign on acetaminophen did not appear to have a significant impact on the problem, so the likelihood of success of an FDA-led educational campaign may be questioned. Although the 2004 effort was substantial, the working group's public education recommendations are more comprehensive than was the earlier effort.
- A second challenge is identifying the appropriate message about the relative safety of acetaminophen, especially compared to other OTC pain relievers (e.g., aspirin and other NSAIDs).[29] Chronic use of NSAIDs is also associated with significant morbidity and mortality. NSAID gastrointestinal risk is substantial, with deaths and hospitalization estimated in one publication as 3200 and 32,000 per year respectively.[30] Possible cardiovascular toxicity with chronic NSAID use has been a major discussion recently.[31] The risks of gastrointestinal and cardiovascular toxicity with NSAID use for less than 10 days are probably much less. Nonetheless, the goal of the educational efforts is not to decrease appropriate acetaminophen use or encourage substitution of NSAID use, but rather to educate consumers so that they can avoid unnecessary health risks.
- Connected with this concern is that some leading manufacturers balk at specific messages (e.g., that acetaminophen may cause severe liver injury) and question the appropriate message about the relative safety of acetaminophen compared to other OTC pain relievers.[32] The media also appear reluctant to disseminate public service announcements that mention specific dangers for advertisers' products.[33]

2. Improve Labeling

Working Group Recommendations: FDA should issue regulations requiring the following labeling:

1. **acetaminophen must be listed prominently on the principal display panel**
2. **the ingredient acetaminophen must be highlighted or bolded in both single ingredient and combination OTC products on the principal display panel**
3. **a warning should be included that severe liver damage may occur if more than the recommended dose is taken**
4. **a warning should be included about not taking the product with other acetaminophen products**
5. **a warning should be included that prompt medical attention after acetaminophen overdose is critical even if consumers do not notice any signs or symptoms**
6. **a warning should be included about concurrent acetaminophen and alcohol use that states a lower daily dose should be used in people who have 3 drinks or more per day**
7. **prominent warnings about liver toxicity should be placed on the immediate containers**[34]

Rationale: As noted in the discussion on increasing educational efforts, improved labeling is also an effective educational tool. The proposed regulations published in the *Federal Register* of December 26,

[29] McNeil has expressed a concern about this issue in the past. *Complaint and Request for Correction Pursuant to the Federal Data Quality Act Concerning "Consumer Campaign on Safe Use of OTC Pain Products"* (May 18, 2004), From *HHS Information Quality Web Site: Information Requests for Corrections and HHS' Re*sponses website, retrieved February 25, 2008, from, http://www.aspe.hhs.gov/infoquality/requests.shtml

[30] Tarone RE, Blot WJ, McLaughlin JK. Nonselective nonaspirin nonsteroidal anti-inflammatory drugs and gastrointestinal bleeding: relative and absolute risk estimates from recent epidemiologic studies. Am J Ther 2004 Jan-Feb;11(1):17-25.

[31] http://www.fda.gov/cder/drug/infopage/COX2/default.htm.

[32] See footnote 29.

[33] Public service announcements in the 2004 educational initiative from FDA were not placed in magazines, and FDA representatives reported to the working group that the publishers took this approach because the publishers did not want to antagonize potential advertisers of paid advertisements.

[34] The immediate or retail container refers to the actual package or container in which the consumer receives the drug. *Cf.* 21 CFR 201.17, 201.62, 201.66, 201.305, 201.314, 201.320, 201.323, 211.132, 211.170, 250.250, 310.509, 310.518, 328.50, 361.1 (provisions using "immediate container" or similar terms in context of drug packaging).

2006 include all the above recommendations except the last concerning immediate containers (see Appendix C for complete acetaminophen-specific language) and identifying an appropriate dose for people who have 3 or more drinks per day.[35] Several entities have supported these labeling changes.[36] Although the immediate container recommendation was not included in the proposed regulation, at least one comment asked that the proposed liver injury warning be required on the immediate container.[37] The working group recommends that this requirement be included in the final rule. This addition may be one of the most important methods of educating the public about the risks related to the use of these products, since consumers may quickly discard other labeling (e.g., carton, package insert).

Mechanisms to Implement and Suggested Timeline: The working group recommends that FDA seek to expedite the post-CDER clearance process for the final rule. Implementation is likely to take a minimum of six months after the final rule is published.

Challenges to Implementation:

- The working group recognizes that acetaminophen may be a difficult name for lay audiences and considered whether APAP should be the name placed on all products instead.[38] The working group, however, rejected this suggestion, because it would not be consistent with all of the information currently available to consumers and patients who use this product (although identifying APAP as another name for acetaminophen may be part of the public education effort). For example, information about acetaminophen in the FDA regulations, on the internet, in advertising, in textbooks and in articles written over the past decades would continue to refer to acetaminophen. In addition, it is somewhat easier to conduct web and other searches for "acetaminophen" than "APAP," since the latter yields sources that have nothing to do with acetaminophen.

- Industry is likely to resist the content of certain label changes, with allegations that data do not adequately support the need for a change. For example, industry has questioned: (1) referring to liver damage as "severe," and (2) the need for a separate liver warning rule proposing liver injury warnings on OTC products from one major manufacturer who does not believe a separate liver warning is necessary.[39]

- Industry may also resist because of costs incurred in changing labels (although relatively minimal compared to other types of changes, e.g., reformulation).

3. Limit Maximum Adult Daily Dose

Working Group Recommendation: Reduce the recommended adult maximum daily dose from 4 grams per day to 3250 milligrams (mg). For chronic alcohol users, the label should recommend a dose lower than 3250 mg (amount not specified).

[35] The Drug Facts labeling is required on the outer cartons. Many drug products are packaged with outer cartons. For products with outer cartons, the immediate container would not have to include the liver warning. 71 FR 77314-52 (December 26, 2006). For the rulemaking history for OTC Internal Analgesic Drug Products, see FDA's Web Site, *Rulemaking History for OTC Internal Analgesic Drug Products,* retrieved February 25, 2008, from http://www fda.gov/cder/otcmonographs/category_sort/internal_analgesic.htm.

[36] For example, the American Academy of Family Physicians, American Association For The Study Of Liver Diseases.

[37] Comment EC2 from Dr. Ijeoma Eleazu, Health Professional.

[38] APAP = N-**a**cetyl-**p**-**a**mino**p**henol. APAP is an abbreviation often used on prescription products. OTC products are not permitted to include this abbreviation.

[39] McNeil submission to the December 26, 2006 proposed rule (71 FR 77314).

Rationale: Although an acetaminophen manufacturer asserts that "data do not support the assertion that repeated, supratherapeutic ingestions of less than 10 g/day present a risk for hepatic injury",[40] the AERS data and the database of the ALFSG show that doses closer to 4 grams per day, the current maximum daily dose, present a risk for some individuals.[41] A recent study[42] showed reversible transaminase elevations in 40% of people ingesting 4 grams per day over several days. The clinical relevance of this finding is unknown. Although most people appear to tolerate 4 grams per day without significant liver injury, it is difficult to ignore the reported cases of liver injury where the total daily dose ingested is close to the daily recommended dose. The toxicity of acetaminophen is the result of a toxic metabolite and individuals could differ, as alcohol users appear to, in how much of it they form, so that it is possible that some people are at increased risk for toxicity. If we could identify these risk factors, they could be provided on the label and people at risk warned not to use the drug or use it in smaller amounts. As long as there are convincing cases at these doses, it is reasonable to recommend a lower daily dose for all users. Moreover, the lower dose will make it less likely that use of more than one acetaminophen product will lead to a toxic dose. Acetaminophen is different from other OTC pain relievers in that the maximum total daily dose limit for acetaminophen is the same for OTC and prescription products. For NSAIDs, the total daily OTC dose is considerably less than the prescription dose. Doubling the maximum daily dose of OTC acetaminophen for several days presents significant risk of developing liver toxicity. In contrast, doubling the maximum OTC dose of NSAIDs for several days exposes consumers to a prescription-level dose, which only slightly increases the risk of gastrointestinal bleeding and "is not even close to the seriousness presented by doubling the dose of acetaminophen."[43]

The narrow therapeutic-to-toxic ratio is particularly troublesome because, as noted earlier, surveys indicate that people routinely and knowingly take more than the recommended dose of OTC pain relievers. Several organizations support reducing the adult maximum daily dose to less than 4 grams.[44]

The working group arrived at the recommendation for the 3250 mg maximum dose per day because it is the total daily dose that results from five single doses of 650 mg (discussed in II.A.4), a dose known to be effective. For some populations, 3250 mg may still be too high.

In the past, FDA has reduced the total daily dose when safety is improved and efficacy is maintained.[45] Lowering the total daily dose will increase the margin of safety of acetaminophen.

Through rulemaking, the agency has already identified chronic alcohol use as a risk factor for acetaminophen toxicity and had labeled acetaminophen accordingly.[46] This position, however, has not

---

[40] McNeil submission to the December 26, 2006 proposed rule (71 FR 77314).

[41] In AERS database and the ALFSG study, the median daily dose of acetaminophen related to liver injury was 5 – 7.5 gram per day.

[42] Watkins PB et al. Aminotransferase Elevations in Healthy Adults Receiving 4 Grams of Acetaminophen Daily. JAMA 2006 Jul 5; 296(1); 87-93.

[43] *HHS Response to FDQA Request for Correction* at 5 (RFC)(August 24, 2004), available at http://www.aspe hhs.gov/infoquality/requests.shtml [hereinafter HHS Response to McNeil FDQA Complaint]; *HHS Response to FDQA Request for Correction* (RFC)(March 7, 2005), retrieved February 25, 2008, from http://www.aspe hhs.gov/infoquality/requests.shtml [hereinafter HHS Response to McNeil FDQA Request for Reconsideration].

[44] AASLD and Arnold and Porter submissions to the proposed rule. Internal Analgesic, Antipyretic, and Anitirheumatic Drug Products for Over-the-Counter Human Use: Proposed Amendment of the Tentative Final Monograph: Required Warnings and Other Labeling, 71 FR 77314-52 (December 26, 2006)(Docket No. 1977N-0094L) (amending 21 CFR 201.66, 201.322, 201.325, 343.50) [hereinafter Proposed OTC Regulations].

[45] Zidovudine (AZT) was decreased from 1000 mg per day (200 mg five times per day) to 600 mg per day (300 mg twice a day). Accutane was decreased from 2 mg/kg/day to .5 – 1 mg/kg/day. Estrogen dose for contraception or menopausal symptoms was reduced because of safety concerns.

[46] 21 CFR 201.322.

prevented some manufacturers from continuing to advocate the same daily dose for chronic alcohol users and non-alcohol users. It is difficult to identify the safe dose in the alcohol user population but it appears that some of these individuals can develop liver injury at the 4 gram dose. If the recommended dose remains 4 grams per day, then alcohol users should use less than 4 grams of acetaminophen per day. If the recommended dose becomes 3250 mg, we would still suggest that labeling recommend a lower dose in alcohol users.

Mechanisms to Implement and Suggested Timeline: The mechanism for these changes is the usual rulemaking process (which also includes label changes to reflect the substantive change). We propose that drafting the proposed rule begins in the next 6 months and that the document be a high priority for clearance.

Challenges to Implementation: The main challenges may be:

- Industry is likely to assert that the 4 grams a day dose is generally safe for most people, and is more effective than the lower doses, so that decreasing the total daily dose for everybody is not an appropriate mechanism to decrease the events in the few at risk even at current doses. One manufacturer argues that there are no populations at risk from the 4 gram dose and for the cases reported it is not possible to identify the true dose that someone ingested.[47] FDA acknowledges the difficulty of defining a safe daily dose and relying on case reports. There are, however, two different databases[48] that suggest toxicity may occur in some people with doses close to 4 grams per day. The data the manufacturer offers to support its assertion is not sufficient to identify a total daily dose with an acceptable risk level.[49] In the past when populations at risk for serious side effects could not be identified, FDA proposed removal of the product from the market (e.g., phenylpropanolamine).[50] Phenylpropanolamine was different from acetaminophen in that there were alternative products available that did not seem to have the same risk of hemorrhagic stroke as did phenylpropanolamine. The reason not to take acetaminophen off the market is that it offers OTC pain relief without some of the risks of NSAIDs particularly in long-term use. This approach (allowing the product to be available at a lesser daily dose) is consistent with adjusting the dose after some side effects for some populations become known after marketing.
- Industry may challenge the view that a sufficiently high percentage of consumers exceed the maximum daily recommended dose.
- There is limited FDA precedent for reducing the maximum daily dose of OTC products, but, as noted, this has been done for prescription drugs and was done to reduce the risk of relatively rare events (deep vein thrombosis with higher estrogen oral contraceptive drugs, hypokalemia and arrhythmias with high dose diuretics).
- Industry may challenge the costs of label change (but they are relatively low compared to other changes, e.g., reformulation changes)

4. Limit Tablet Strength and Single Adult Dose

Recommendation: Reduce tablet strength for immediate-release formulations to 325 mg (or less) and limit the single adult dose to 650 mg (or less). Limit tablet strength for extended-release formulations commensurate with total daily dose and the dosing increment.

[47] Page 9 of summary: McNeil submission to December 26, 2006 proposed rule (71 FR 77314).
[48] In AERS database and the ALFSG study, the median daily dose of acetaminophen related to liver injury was 5 – 7.5 gram per day.
[49] Daly FS, O'Malley GF, Heard K, Bogdan GM, Dart. Prospective Evaluation of Repeated Supratherapeutic Acetaminophen (Paracetamol) Ingestion. Ann Emerg Med. 2004;44:393 – 398.
[50] 75988 Federal Register / Vol. 70, No. 245 / Thursday, December 22, 2005.

Rationale: Decreasing the maximum individual dose from 1000 mg to 650 mg will decrease the daily exposure of acetaminophen without much loss of efficacy. Although some studies suggest the increased efficacy of 1000 mg compared to 650 mg, they are few and limited to specific uses and the difference is small.[51] OTC pain medication (e.g., ibuprofen, naproxen) are regularly labeled to be given at single and daily doses that are lower than the maximum effective dose. As noted in the previous discussion on the benefit of decreasing the total daily dose, however, decreasing the tablet strength will also affect those individuals who take more than the recommended number of tablets intentionally or unintentionally. For example, people who take two tablets of two different products with each tablet containing acetaminophen 500 mg, they would be exposed to 2 grams per dose (1 gram from each product). If only 325 mg tablets were available for adults, the exposure with such dosing would be 1300 mg per dose. Over the course of a day, assuming 4 doses, exposure would be 5200 mg versus 8000 mg. This alone would lead to fewer cases of hepatotoxicity even if people continued to take two products at the same time. This intervention will also reduce the acetaminophen exposure of those who take more than the recommended number of tablets of a single product.

Limiting the tablet strength for immediate-release formulations to 325 mg (or less) and the single adult dose to 650 mg (or less) could be considered separately from measures to reduce the total daily dose of acetaminophen. However, limiting both the tablet strength and single dose should provide a wider safety margin and should reduce the incidence of hepatotoxicity. Even if acetaminophen were dosed 5 times daily, instead of the current four times daily, the total daily dose would be 3250 mg, which is 19% less than the current 4000 mg maximum daily dose.

The working group noted that, while limiting the tablet strength and single dose is aimed primarily at reducing unintentional overdose, it might also reduce the risk or severity of hepatotoxicity due to an *intentional* overdose. In an intentional overdose, if all the pills in a bottle contain less acetaminophen, the chance of a fatal or other serious outcome might be reduced because more pills would be required to achieve the same level of exposure. It would, however, have little impact if the number of pills ingested was 50 tablets or greater.

In the past, FDA has reduced single doses when safety is improved and efficacy is maintained.[52] In this situation, we have only limited data suggesting that efficacy is better with the 1000 mg dose than the 650 mg dose and any difference is very small. The 650 mg dose is clearly an effective analgesic. Lowering the dose will increase the margin of safety.

Mechanisms to Implement and Suggested Timeline: The mechanisms are the same as those for the maximum daily dose recommendation above, except that further legal research may be required to determine the appropriate method for requiring certain tablet strengths, as those are generally not specified by monographs.

[51] See p. 44 ONP review, p. 6 OSE review, data are few that show a single dose of 1000 mg is more effective than a single dose of 650 mg for *pain relief*; in the NDA approval for Tylenol capsules 500mg (NDA 17-053 in 1973), two studies of patients with post-episiotomy pain showed marginally greater effectiveness for 1000 mg vs. 650 mg; however, two similar pain-relief studies showed no greater effectiveness of 1000 mg vs. 650 mg; while it is likely that acetaminophen is used more often for pain relief than for *fever reduction* there are no data showing greater effectiveness of 1000 mg vs. 650 mg for fever reduction; literature also suggests that some putative factors leading to a greater risk of hepatotoxicity include prolonged fasting and a concomitant viral infection, both of which may accompany febrile conditions; recent protocols studying acetaminophen have excluded subjects who are on a fasting diet).

[52] The recommended hydrochlorothiazide dose has been reduced from 100 mg per day to 25 mg and even 12.5 mg is a dose in some combinations. Chlorthalidone has been similarly reduced. The dose of Halcion has been reduced to improve safety. Estrogen dose for contraception has been gradually reduced to decrease thromboembolic risk. The dose of digoxin has moved gradually down from 0.5 mg per day. All of these examples are single daily doses for these medications.

Challenges to Implementation:

- Manufacturers seem very likely to challenge this step, principally because the 500 mg tablets constitute a large portion of sales. Changes in tablet strength may have the greatest impact on companies that do not have a 325 mg tablet, since that will entail costs of formulation changes.

- Manufacturers may argue that there are adequate data supporting greater effectiveness of 1000 mg vs. 650 mg. However, as noted previously in the section on decreasing the total daily dose, if there is any greater effect at the higher dose the difference is small and use of the 1000 mg single dose administered four times represents a dose that is right at (or above for some people) the safe limit because acetaminophen is a narrow therapeutic margin drug. A wider safety margin is needed for acetaminophen. Moreover, for all other OTC analgesics, the OTC dose is well below the maximum dose.

- Manufacturers are likely to assert that there is minimal risk in a 500 mg tablet strength or 1000 mg single dose, provided that a maximum ceiling of 4000 mg per day is not exceeded. [53] Although we agree that the 1000 mg dose is tolerated by most people, some do not tolerate it. Moreover, people still use more than recommended or use more than one product containing acetaminophen. Current warnings of overdose and labeling identifying products containing acetaminophen have not adequately decreased the number of serious cases of liver injury.

- There are a limited number of OTC single ingredient products containing 325 mg tablets of acetaminophen. Some companies will have to reformulate and conduct additional stability testing.

5. Limit Options in Liquid Formulations

Working Group Recommendation:

(1) Limit pediatric[54] acetaminophen liquid formulations to one mid-strength concentration
(2) Require that measuring device be included in each package
(3) Include dosing instructions for children under 2 years

Rationale: The first recommendation is based on data showing that acetaminophen overdoses occur because caregivers make dosing errors by confusing the different formulations and incorrectly giving children the more concentrated infant drops but using amounts appropriate for the less concentrated formulations.[55] If a household has an infant and another small child, then there could be more than one acetaminophen liquid preparation in the household, requiring that a caregiver select the correct dosage form in addition to the correct volume to administer. Some acetaminophen manufacturers (e.g., McNeil) began changing their advertising and labeling to reduce the confusion, but the working group is not aware of data indicating that these efforts have reduced the problem.

---

[53] McNeil submission to the December 26, 2006 proposed rule (71 FR 77314).

[54] Unless otherwise indicated, *pediatric* refers to children age 12 and younger, and includes infants and neonates.

[55] See p. 21, ONP Review, 544 of 1730 calls involving acetaminophen exposure in children 0-11 years of age to two Poison Control Centers for the year 2000 were due to maladministration; the majority of these calls involved two specific single-ingredient acetaminophen liquid formulations: Infant Tylenol Concentrated Drops and Children's Tylenol Suspension or Elixir; **See** p.2 , ONP Options Table, two thirds of parents who bought their child under the age of 7 years to an urban pediatric emergency department did not know the difference between concentrated infant drops and other liquid preparations of acetaminophen; Barrett TW, Norton VC. Parental knowledge of different acetaminophen concentrations for Infants and Children. Academ Emerg Med. 2000 Jun 7; 7(6): 718-21.

Based on this information as well as the lack of evidence that voluntary changes in labeling and public education have reduced the errors, the working group concluded that there should be a single liquid acetaminophen concentration. The working group also proposes that the one formulation be a mid-strength concentration (i.e., be less concentrated than 80 mg/0.8 ml concentrated infant drops and closer to or equal to the suspension liquid concentration of 160 mg/5 ml).

Another source of errors in dosing liquid acetaminophen preparations is use of an *incorrect dosing device* to measure the medication, which can have significant adverse effects given acetaminophen's narrow therapeutic-to-toxic window discussed above.[56] A dropper is attached to the bottle of Infant Concentrated Drops. The liquid suspensions have labeling that gives doses by teaspoon or milliliters, but a measuring device is not required to be included in the package. Spoons can vary considerably in volume. Dosing errors have occurred when a household teaspoon has been used to dose Infant Concentrated Drops to an older child and when a health professional has ordered the dose in teaspoons.[57] The working group thus recommends that an appropriate measuring device be included in liquid formulations with appropriate labeling. A recent advisory committee evaluating the safety and efficacy of ingredients for the common cold recommended standardization of dosing devices. Our recommendation for acetaminophen is in line with this recommendation and is a reasonable way to prevent unintended dosing errors.[58]

A third type of dosing error occurs with children under 2 years of age because the monograph allows dosing of acetaminophen for children down to 2 years, with instructions to consult a health professional for dosing instructions for children under 2 years. [59] In a Citizen Petition, McNeil Consumer Healthcare has requested dosing of the Infant Concentrated Drops down to 2 – 4 months of age. [60] FDA is considering the merits of the petition. For infants 4 months of age to children up to 3 years of age, *both* the Infant Concentrated Drops and the Children's Suspension Liquid have an advertised dosing regimen in the Physician's Desk Reference for Nonprescription Drugs and Dietary Supplements.[61] FDA has not approved a specific acetaminophen dosing regimen for children below 2 years of age. This overlap in advertised, but unapproved, dosing could cause confusion and lead to medication dosing errors. In the absence of a *single concentration* with dosing from a monograph or other approved drug, there is an added risk of a caregiver giving an improper dose of acetaminophen for children less than 36 months of age.

Mechanisms to Implement and Suggested Timeline: Usual rulemaking is the mechanism for this recommendation. These recommendations should be added to the pediatric dosing rule that is currently being revised, with the usual rulemaking timeline to follow.

Challenges to Implementation:

- Industry may resist costs of reformulation and possible loss of revenue if certain products are eliminated
- Consumers may resist more limits on choice of formulations.

[56] See p.5, ONP Review.
[57] See p. 10 OSE review by Claudia Karwoski 2002; see p. 8 OSE review Carol Holquist 2006.
[58] October 18, 19, 2007. Joint meeting NDAC/PDAC meeting of Nonprescription Drugs Advisory Committee and Pediatric Drugs Advisory Committee**.** Discussion of the safety and efficacy of cough and cold products in the pediatric population.
[59] Tentative Final Monograph: Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use**;** 53 FR 46204 November 16, 1988, to be codified at 21 CFR 343.50(d)(2).
[60] Citizen Petition submitted by McNeil Consumer Healthcare, Docket No, 77N-0094 (In FDA AIMS application, listed as 1977-0094), Document ID No. CP14 (Feb. 1, 1999).
[61] McNeil Consumer Healthcare advertisement in PDR for Nonprescription Drugs 2007; Table 1, p. 757-8.

- Industry may challenge the strength of the supporting data (e.g., (1) extent to which the number of liquid formulations, lack of measure device, lack of dosing instructions for children under 2 years creates safety concern, (2) effectiveness of public education on pediatric liquid formulations).
- The working group acknowledges that if only *one concentration* of liquid acetaminophen were available, e.g., if Concentrated Drops were eliminated, then the large volume of liquid required for dosing of infants could be a problem. To assess the impact of an increased volume delivered to the populations most affected by medication volumes, a member of the working group contacted an attending physician in the neonatal intensive care unit at Children's National Medical Center, Washington D.C. (CNMC), who then consulted other staff members.[62] The staff at CNMC indicated that they do not typically use infant concentrated drops for treating neonatal[63] pain because morphine is usually the drug of choice for pain relief. Acetaminophen is not used often for fever control because the staff generally follow the patient's fever. Acetaminophen concentrated drops are used after minor procedures such as immunization, but the staff was unsure about whether use of the less concentrated formulation would result in giving too much volume to neonates and thought this question could only be answered through time. They also questioned whether any inactive ingredients (e.g., propylene glycol, purified water, sodium benzoate, or sorbitol) would cause problems in larger volumes. This information from the CNMC suggests that use of a single less-concentrated liquid formulation of acetaminophen poses some questions or issues, but not insurmountable problems, in providing analgesia or fever reduction in neonates.
- The Agency would also need to evaluate whether any changes concerning acetaminophen products would also apply to other liquid pediatric formulations that raise similar concerns about dosing errors.

6. Eliminate Combination Products

Working Group Recommendation (with one dissent): Eliminate acetaminophen from all OTC combination products.

Rationale: The use of combination products containing acetaminophen is a convenience for consumers. OTC acetaminophen combination products account for significant amount of product sales.[64] About half of the sales of OTC acetaminophen products are combinations.[65] Although consumers may recognize the presence of acetaminophen in a combination with Tylenol as part of the name, they may be less likely to recognize acetaminophen in other combinations. This can lead to the concomitant use of multiple acetaminophen-containing products Even though the percentage of cases of acute liver failure resulting from the use of two OTC products is relatively low (as discussed below), it is difficult to justify any cases because these products are available only for convenience.

In 2005, there were 67,531 exposures reported to the Toxic Exposure Surveillance System (TESS) for OTC acetaminophen single-ingredient products, and 7,083 (or 10.5% as many) exposures for OTC acetaminophen combination products.[66] Also in 2005, there were 72 death cases recorded in the AERS database associated with use of acetaminophen-containing products. Eighty-one acetaminophen products

[62] Teleconference and emails between SO (FDA) and LS (CNMC) May 2007.
[63] Neonates are up to 4 weeks of age.
[64] These combinations are governed in part by 21 CFR 341.40 (permitted combination of active ingredients in OTC products, specifically including acetaminophen). From Laura Governale review on use: Between 2001 and 2005, 24 – 29 billion doses of acetaminophen (in all forms) were sold. OTC accounted for 60 – 68% of the sales by number of doses. One-half of the OTC sales were for combination products.
[65] See p. 3, OSE review of OTC and Rx acetaminophen use by L. Governale, November 2006. Data from 2001-2005.
[66] See pp. 36-37 OSE review.

were reported in these 72 deaths, with 5 reports (6%) involving OTC combinations, 27 reports (33%) involving single ingredient OTC acetaminophen products, and 49 reports (60%) involving prescription combinations.[67]

Data from the ALFSG indicate that out of 275 patients with acute liver failure due to acetaminophen, 147 patients ingested only OTC acetaminophen products. Of these 147 patients, 141 (96%) used a single product and 6 (4%) used two OTC products.[68] It is not clear from the published ALFSG report whether the people who used only one OTC product used a single ingredient or combination product. The working group was not aware of the percent of cases of acetaminophen hepatitis that may be attributable to a single ingredient product or to a combination product.

The working group recognized that consumers may find a combination product easier to use to treat multiple symptoms, but also noted that these are products used for convenience for which safe alternative products are also available and that there are many occasions when all of the ingredients of the combination product are not needed. In particular, the consumer might need a decongestant or antihistamine, or both, but would not need acetaminophen for fever reduction or pain relief. If fever or headache developed later, then taking another acetaminophen-containing product could lead to an acetaminophen overdose.

Mechanisms to Implement and Suggested Timeline: See maximum daily dosage recommendation above.

Challenges to Implementation:

- Data may not be sufficiently conclusive that OTC combination products are responsible for a significant percentage of acetaminophen overdoses
- The economic impact with regard to sales data would be substantial.
- There may be a charge of inconsistency if FDA supports eliminating OTC combination products while not supporting eliminating prescription combination products.
- Manufacturers and consumers may oppose removing these popular products, especially in light of the evidence that OTC combination products are responsible for a relatively small percentage of all acetaminophen overdoses. This FDA intervention thus could create a response that FDA is overreacting with a drastic measure based on uncertain data and before other less drastic interventions have been tried. Based on these concerns, one working group member dissented from the recommendation to remove OTC acetaminophen combination products. This member felt that the risks of making this recommendation at this time did not outweigh the benefits, instead advocating that FDA put stakeholders on notice that removing OTC acetaminophen combination products was a serious future option if the other recommendations were implemented and found not to be successful. The remainder of the working group acknowledged these points but still felt this intervention is an important part of any program to reduce unintentional overdoses and that the benefits of eliminating the combination products (decreasing the likelihood of concomitant use of two or more acetaminophen OTC products, thus decreasing the chance of unintentional overdose) outweighed the possible negative consequences described above.

[67] See p. 24-25 OSE review. It is worth noting that other drugs could have been co-ingested in these cases.
[68] See p. 12 ONP review; data from Larson AM, Polson J, Fontana RJ, Davern TJ, Lalani E, Lee WM et al. Acute Liver Failure Study Group (ALFSG). Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. Hepatology 2005 Dec;42(6):1364-72.

7. Identify Further Research Needs

Working Group Recommendations: Identify currently existing research or consider conducting further research to address important issues that do not appear to have been adequately addressed, including research identifying:

- **specific patient populations especially susceptible to acetaminophen hepatotoxicity**
- **the appropriate acetaminophen dose for populations that may be most susceptible to liver injury**
- **the best ways to evaluate success of efforts to reduce acetaminophen overdoses and hepatotoxicity**
- **the best databases to identify acetaminophen overdose and hepatotoxicity, including databases that capture injury less significant than liver failure**
- **the extent to which specific types of products (e.g., combination, 500 mg, extended-release) cause liver injury**
- **the effect of reduction of acetaminophen use on other drug use (to determine if interventions push people to decrease the use acetaminophen and increase the use of NSAIDs)**
- **the level of consumer awareness of acetaminophen hepatotoxicity and best methods to communicate risks and benefits to consumer**
- **explore further the observations by Watkins, et. al. , that 40% of people given 4 grams/day of acetaminophen have aminotransferase elevations. It would be of interest to examine dose response for this observation and look for differences in extent and duration of injury and for possible interactions with other drugs and individual metabolic differences.**

Rationale: FDA will have to continue to follow the incidence of acetaminophen hepatotoxicity after any measures are implemented. It will be important to identify databases now to determine a baseline occurrence rate and continue to monitor them in the future after any interventions are implemented. The incidence data will need to be followed over the next several years to determine whether the interventions were effective in decreasing the number of cases.

The reviews from DAARP, OSE and ONP identified much in the literature regarding acetaminophen hepatotoxicity. There are however, areas that need further investigation. The working group identified topics requiring additional research. Collaboration with other government agencies and academia will help to further identify other areas of research.

Mechanisms to Implement and Suggested Timeline: Current CDER staff could continue to identify relevant databases, monitor the databases and continue literature searches for new information in the literature. In addition, the working group recommends that the FDA work with other government agencies and academia to identify research priorities to address some of the factors that may increase the risk or contribute to the risk for toxicity. The research should be directed at identifying risk factors for injury, appropriate dosing for susceptible individuals, consumer use of the products and mechanisms to decrease the occurrence of hepatotoxicity. The CDER Director can decide how this should proceed. An interagency working group may be one option.

Challenges to Implementation: The main challenges are limits on financial resources available to conduct research and the time commitment necessary from internal staff with large workloads.

8. Recommendations Considered But Rejected

The working group considered the following recommendations but chose to reject them.

(1) Put some OTC acetaminophen products (e.g., 500 mg tablets, concentrated infant formulas) behind-the-counter or switch to prescription status: The working group chose not to make either of these recommendations at this time because the status of behind-the-counter medications is currently undergoing review. The working group also felt that there was not adequate evidence that a prescription option was viable (e.g., that it would be sufficiently appealing to consumers and manufacturers) and was concerned that a major switch to NSAIDs for treatment of chronic pain in people now using acetaminophen would not represent a safety gain.

(2) Restrict Package Size: The working group considered recommending package size restrictions for OTC acetaminophen products. Consideration of this intervention is based on the experience in the UK[69] in its attempt to limit the cases of intentional overdose with acetaminophen. The restrictions in the UK are erroneously characterized as package size restrictions in some publications but they are actually a sale restriction. Packages of sixteen 500 mg tablets for general sale or thirty-two 500 mg tablets for sale by a pharmacy reflect the maximum number of tablets that can be sold at each location without a pharmacist. The UK experience has been documented in numerous studies [70] with most suggesting that the number of cases of severe liver injury were reduced. There are, however, some publications suggesting that there has been no decrease or that the data is insufficient to make any conclusions about the effect.[71] Although the UK intervention was intended to address intentional overdose, there was some reduction in the number of cases of unintentional overdose.[72]

There was uncertainty about the appropriate regulatory approach to limit the number of packages sold of an OTC drug product to a single consumer. If a sale restriction is not feasible, there appear to be limited potential benefits associated with restricting the package size in the United States for OTC acetaminophen products while continuing to allow consumers to purchase unlimited numbers of packages. This approach would differ considerably from the UK model. Also, there is concern that the cost of the product would increase considerably. This increase would not pose a significant new problem to many people who already purchase limited quantities on a regular basis, but it would impose an unnecessary cost burden on patients, primarily the elderly, who use acetaminophen daily for chronic osteoarthritis. The working group discussed whether larger quantities could be purchased through a pharmacist but determined this approach would be unprecedented in the United States. Because of these concerns, the working group did not recommend packaging restrictions.

Some working group members felt that package restrictions might be of some benefit, but unless the UK model was followed, they acknowledged it would be difficult to justify limiting package size amounts. The working group discussed mandating blister packaging for all products that contain acetaminophen. It has been suggested that blister packs have played a role in helping to decrease the number of cases of intentional overdose leading to hepatic toxicity.[73] Blister packs are not required in the UK but many manufacturers used them once the sales restrictions for the general sale of acetaminophen were mandated. It is not clear, however, what role blister packaging has played in decreasing cases of intentional liver injury in the UK because multiple interventions were initiated at the same time (e.g., sale restriction,

---

[69] See p. 30 – 36 in ONP review and p. 33 – 34 in OSE review.

[70] See table 12 on p. 33 – 34 in ONP review. Hawkins LC, Edwards JN, Dargan PI. Impact of restricting paracetamol pack sizes on paracetamol poisoning in the United Kingdom: a review of the literature. Drug Saf 2007; 30: 465-79.

[71] Bateman DN, Gorman DR, Bain M, Inglis JH, House FR, Murphy D. Legislation restricting paracetamol sales and patterns of self-harm and death from paracetamol-containing preparations in Scotland. Br J Clin Pharmacol. 2006 Nov;62(5):573-81. Morgan O et al. Paracetamol (acetaminophen) pack size restrictions and poisoning severity: time trends in enquiries to a UK poisons centre. J Clin Pharm Ther 2007; 32: 449-55. Hawkins LC, Edwards JN, Dargan PI. Impact of restricting paracetamol pack sizes on paracetamol poisoning in the United Kingdom: a review of the literature. Drug Saf 2007; 30: 465-79.

[72] Presentation by Dr. William Bernal; Acute Liver Failure National Institute of Health Workshop, December 4 -5, 2006.

[73] Turvill JL, Burroughs AK, Moore KP. Change in occurrence of paracetamol overdose in UK after introduction of blister packs. Lancet. 2000 Jun 10;355(9220):2048-9.

package insert describing liver injury). The working group does not recommend that blister packaging be the only type of packaging permitted. The working group believes that blister packages could be difficult to open for individuals who use acetaminophen for conditions such as osteoarthritis. Such people, who would in many cases need 8 – 10 tablets a day, would also face significant inconvenience, again perhaps driving them to NSAID alternatives, not the intended outcome. Blister packaging should be left as an option for the manufacturer.

(3) Include specific additional maximum daily dose restrictions for consumers with liver disease. The working group concluded that there was not adequate evidence at this time to make a specific recommendation for consumers with liver disease, but recommends that additional research be conducted to address this issue.

(4) Require additional patient-directed written inserts: Patient package inserts are not commonly used in OTC products and are typically limited to explaining how to use the product, not to provide additional information about adverse events.[74] It is not clear that this requirement would have much of an impact on decreasing the risk for liver injury.

(5) Change the name Acetaminophen to APAP: The working group considered this option but had concerns that this step would not provide a solution to the current problem. Medical textbooks/literature and information on the internet would continue to use the name acetaminophen. Consumers or patients seeking information would be less likely to find information searching for the term APAP.

(6) Include the name paracetamol on the acetaminophen-containing products: Since acetaminophen is referred to as paracetamol in many countries outside the United States, some groups suggested that paracetamol be included in the label and elsewhere (e.g. USP monographs).[75] The working group chose to recommend against including paracetamol in the label (independent of any legal concerns) because the label is already lengthy and there is not adequate evidence that safety issues have arisen because of this omission.

B. Prescription (Rx) Product Recommendations

Prescription acetaminophen combination products[76] are one of the primary causes of both unintentional and intentional acetaminophen overdose leading to hepatotoxicity.[77] Although many of the issues about acetaminophen hepatotoxicity are the same for prescription products as they are for OTC products, there are some important differences between the two groups. First, the prescription combination products contain opioids/narcotics, so patients and providers may focus primarily on risks associated with opioids (e.g., respiratory depression, abuse and addiction) and underestimate the risks associated with acetaminophen. Secondly, patients may develop worsening pain or tolerance to the narcotic, creating a need to increase the narcotic dose; if they are taking combination acetaminophen Rx products, this tolerance will also increase their acetaminophen intake, which serves no therapeutic purpose but increases the risk of liver injury. The working group recommends the following interventions to reduce hepatotoxicity from prescription acetaminophen products: (1) enhance public education efforts, (2)

[74] Example: Today's Sponge.
[75] See, e.g., Letter from Anthony Palmieri III, United States Adopted Name (USAN) Council (AMA) dated July 31, 2007 to Yana Mille, CDER.
[76] The prescription acetaminophen products are mostly in combination with a narcotic.
[77] Larson AM, Polson J, Fontana RJ, Davern TJ, Lalani E, Lee WM et al. Acute Liver Failure Study Group (ALFSG). Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. Hepatology. 2005 Dec;42(6):1364-72.

improve labeling, (3) require unit-of-use packaging, (4) limit the maximum daily dose, (5) limit the permitted tablet strength and recommended adult single dose, and (6) identify further research needs.

The mechanisms and timelines for prescription products differ from the OTC products in that the first step the working group suggests for most Rx recommendations is a uniform supplement request letter requesting labeling modifications and other changes (see below) that would be sent to all acetaminophen NDA holders. Most of the products are also marketed under ANDAs. Once changes are agreed upon then ANDA holders will need to be notified. NDA/ANDA letters will require a significant amount of work by project management staff. In addition, reviewing submissions for some types of requested changes (e.g., chemistry and labeling supplements, change in tablet strength and unit-of-use packaging, both requiring stability testing) will require significant resources in CDER.

1. Enhance Public Education Efforts

As noted previously, research indicates that consumers are often unaware that their prescription combination products contain acetaminophen. The public education discussion in the OTC section of the report generally applies to the Rx products as well.

2. Improve Labeling

Working Group Recommendations:

(1) Include a standard hepatotoxicity warning and prominently display acetaminophen as an active ingredient on the immediate medicine container
(2) Include a Medication Guide[78] focusing on the risk of hepatic injury
(3) Modify professional labeling to include a boxed warning and make acetaminophen hepatotoxicity warnings at least as strong as OTC warnings
(4) Require that acetaminophen appear on the container dispensed to the patient and not permit the abbreviation APAP

Rationale: The working group's labeling recommendations for prescription products are designed to better inform consumers, as well as health professionals, about acetaminophen hepatotoxicity. Labeling for prescription drug products differs significantly from OTC labeling. While OTC labeling is designed for consumers, most prescription labeling is designed for the prescribing health professional or pharmacist. Furthermore, OTC packages are made by manufacturers and must comply with specific labeling regulations, as discussed above, but prescription packages that are dispensed by pharmacists ordinarily do not have labeling well designed to be understood by consumers. For prescription products, the name of the active ingredient on the container the patient receives is often abbreviated (e.g., APAP instead of acetaminophen) and warnings on the immediate container are not usually required even for products with strong labeling warnings. There is evidence that warnings may be more effective if the user has to physically interact with them during product use.[79] Surveys show that consumers do not always recognize the presence of acetaminophen in combination prescription narcotic products.[80] Thus, placing the name acetaminophen and a warning on the container itself may increase the likelihood that the user

[78] 21 CFR Part 208. For links to current Medication Guides, see http://www fda.gov/cder/Offices/ODS/medication_guides htm.
[79] Lesch MF. "Consumer Product Warnings: Research and Recommendations." Handbook of Warnings.. Ed. Michael S. Wogalter. Mahwah, N.J.: Lawrence Erlbaum Associates, 2006. Chapter 10
[80] The McNeil Habits and Practices Survey provide relevant data. This survey demonstrates that consumers did not know or could not recall what certain prescription products contained. Only one of 61 consumers who were taking Vicodin, Percocet, or Endocet knew that the product contained acetaminophen. None knew what the other active ingredient was in any of these products. Retrieved February 25, 2008, from http://www fda.gov/ohrms/dockets/ac/02/briefing/3882B1_13_McNeil-Acetaminophen htm

know what ingredient is in the product and will see and heed the warning. If this cannot be accomplished via the current process of distribution, unit-of-use packaging is a consideration that is discussed later in this document. The working group recommends that the immediate container be required to prominently display a warning similar to that on OTC products.

The working group recommends that prescription products also include a Medication Guide describing the risk of hepatic injury, because many patients are not aware of the potential acetaminophen hepatotoxicity or even that the prescription product contains acetaminophen. The additional information should include the following concepts, and be consistent with the message in the OTC warnings, although the working group did not determine whether the wording in OTC and prescription products should be identical. The group recommends that patient-directed information include the following concepts and be consistent with the concepts included on OTC labeling:

- Acetaminophen can cause severe and irreversible liver injury if more than the recommended dose is ingested;
- Acetaminophen is present in many medications so it is important to examine the content of medications and not take multiple medications containing acetaminophen;
- Hepatic injury may take several days to occur and signs and symptoms may not appear before that time
- If you drink alcohol or have underlying chronic liver disease, using acetaminophen may increase your risk of liver injury.

The working group also recommends that the prescription labeling include a "boxed" warning.[81] There are over 200 NDAs and ANDAs listed in the Orange Book that would have to add the boxed warning. The working group discussed whether this intervention would have any impact on the prescribing and use of the products, as well as whether the risks posed by acetaminophen hepatotoxicity are sufficient to warrant a boxed warning. The working group decided it was important to use multiple avenues of communication in conveying the risk to health providers and patients. FDA regulations[82] and a draft guidance[83] describe various situations where a boxed warning should be considered. The situation most applicable to the liver injury caused by prescription acetaminophen medications is: *There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation).*[84]

The working group believes that many of the cases of liver toxicity related to unintentional overdose are preventable if the drug is used appropriately. The drug should not be used with other OTC acetaminophen products or used in amounts that exceed the recommended dose. Patient self-titration should be limited because it may contribute to excess acetaminophen ingestion.

Mechanisms and Timelines for Implementation: The medication and boxed warnings can be created and sent out in uniform supplement request letters within the next 3-6 months. Although the immediate container labeling could also be completed in that time period, the best method for implementation

[81] Working group members were not aware of a place on the FDA website that lists all the drugs for which box warnings are required. However, the MedWatch section lists safety labeling changes, which includes references to "boxed warnings." See http://www fda.gov/medwatch/SAFETY/2007/may07 htm.

[82] 21 CFR 201.57(a)(4)(concise summary of boxed warning); 201.57(c)(1)(FDA may require contraindications or serious warnings, particularly those that may lead to death or serious injury, to be presented in a box and ordinarily must be based on clinical data).

[83] *Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling or Human Prescription Drug and Biological Products — Content and Format*, pp. 9-10 (Draft Guidance January 2006). Retrieved February 25, 2008, from http://www fda.gov/cder/guidance/5538dft htm.[hereinafter Warnings Guidance].

[84] Warnings Guidance, p. 9.

requires additional evaluation. OCC input is needed to identify the legally appropriate and quickest method for implementing the immediate container labeling recommendations. Because the pharmacist rather than the manufacturer is often responsible for labeling the immediate container, OCC would need to ensure that FDA requirements are consistent with FDA authority and do not impermissibly encroach on state provisions about the practice of pharmacy. Options to pursue include disseminating a Guidance or other policy statement (perhaps with a Federal Register notice) that failure to include such warnings on the immediate container constitutes misbranding as a misleading label under the misbranding provisions of the Food, Drug, and Cosmetic Act. [85] Another option is promulgating a regulation explicitly stating that failure to have this immediate container labeling constitutes misbranding.[86]

Challenges to Implementation

- The main challenge to implementing the container labeling is identifying the most appropriate mechanisms for implementation.
- The main challenges to the Medication Guide and boxed warning recommendation are
    - Concerns about the length and distribution of Medication Guides.[87] Despite these concerns, the working group feels that an appropriately compact Medication Guide is one of many mechanisms needed to communicate the risk of hepatic injury from use of prescription combination products.
    - Some will question how a drug with a boxed warning can also be available OTC.[88]
    - Boxed warnings affect how the products are marketed,[89] principally by making reminder ads unacceptable, but this issue may not be important, as most of these drugs are not advertised.

3. Require Unit-of-Use Packaging

Working Group Recommendations: FDA should require Unit-of-Use Packaging to Facilitate Labeling.

Rationale: In addition to requiring a Medication Guide and package labeling on prescription products, the working group recommends that FDA mandate unit-of-use packaging for all prescription acetaminophen products, i.e., requiring that all packages dispensed to the patient be those created by the manufacturer. Such packaging recommendations are designed to enhance the likelihood patients will see a consistent warning on the containers dispensed by the pharmacist and will receive the Medication Guide; it has long been recognized that distribution of Medguides in the absence of unit of use packaging is unreliable. The working group does not recommend any specific type of packaging because manufacturers may be able to create innovative designs, and requiring a single type of package could stifle innovation. It is worth noting that OTC drug products are already packaged in this manner and unit-of-use packaging is the norm in European countries and is already widely used in the United States, packaging of oral contraceptives being a notable longstanding example. Other prescription products are also pre-packaged at the manufacturer's discretion (e.g., Zithromax Z-Pac) with the name prominently displayed, and such packaging is common for many chronically used drugs This approach is generally done at the manufacturer's discretion but FDA has required warnings on the cartons of a variety of products that can

[85] Federal Food, Drug, and Cosmetic Act, sections 502(a), 503(b)(2), codified in 21 U.S.C. 352(a), 353(b)(2).
[86] For similar examples, see, e.g., 21 CFR 201.303, 201.316.
[87] See "Public Hearing on Use of Medication Guides to Distribute Drug Risk Information to Patients June 12-13, 2007," retrieved February 25, 2008, from http://www fda.gov/cder/meeting/medication_guides_200706 htm.
[88] Prescription NSAIDs contain a box warning of cardiovascular risk. OTC NSAIDs contain a warning "long term continuous use may increase the risk of heart attack or stroke".
[89] See, e.g., 21 CFR 202.1(e)(2).

be dispensed to patients.[90] It is not clear, however, whether pharmacists are required to dispense the unit of use package for all products packaged this way i.e. they can repackage these products at their own discretion. If they choose to do so, however, they are legally obligated to dispense the Medguide.

Mechanisms to Implement and Suggested Timeline: Uniform supplement request letters could be sent out within the next 3-6 months, but if manufacturers do not want to make these changes, the usual rulemaking process will be required.

Challenges to Implementation:

- Manufacturers may oppose such requirements as unnecessary, not consistent with FDA's approaches to other medications, and unduly expensive. The approach, however, is consistent with the way all OTC drugs are packaged and the way drugs are packaged worldwide, so that it would be difficult to raise a credible economic obstacle. There will be costs associated with the transition over to unit-of-use packaging but the cost of developing new unit-of-use packaging is met by the over-the-counter drug industry on a regular basis when they bring new products or package sizes to market.
- Some will argue that OTC acetaminophen products use unit-of-use packaging and this alone does not eliminate liver toxicity. This is true, but the current packages of OTC products are not adequately labeled to warn of the risk of liver injury. Unit-of-use packaging and improved labeling together will help identify the ingredients are in the product and educate users of the products.
- There may be additional costs for stability testing unless application holders have data that can be extrapolated to new packaging from the data that supports the current packaging.

4. Limit Maximum Daily Dose

See OTC discussion of limiting maximum daily dose and general caveats above about uniform supplement request letters followed by rulemaking.

5. Limit Tablet Strength and Single Adult Daily Dose

See OTC discussion of limiting tablet strength and single adult daily dose and general caveats above about uniform supplement request letters followed by rulemaking.

6. Identify Further Research Needs

In addition to the research needs mentioned in the OTC section, additional research needs to be identified to determine the extent to which acetaminophen adds to the pain control efficacy of the combination product.

7. Recommendations Considered but Rejected

(1) Replace acetaminophen with APAP: See OTC discussion.

(2) Eliminate Combination Prescription Products (one dissenter): The use of the combination narcotic product is common based on many factors, including limited non-narcotic options, and greater

[90] Fentora (fentanyl Buccal tablet) is packaged in unit of use container (28 tablets) with warning on carton (Warning: Keep out of the reach of children) and medication guide, Rescriptor (delavirdine mesylate) is packaged in unit of use container with "alert" on carton (find out about medicine that should not be taken with Rescriptor). Accutane (isotretinoin) requires warnings on blister pack prescription cards.

restrictions on availability for higher scheduled single-ingredient narcotic analgesics. Narcotic combination products are subject to the controls imposed by their "schedule" classification under the Controlled Substance Act (CSA).[91] Oxycodone/acetaminophen combination products are in Schedule II of the CSA, whereas hydrocodone and codeine combination products are subject to Schedule III controls. Some codeine combination products are Schedule V. These schedules impose various controls regarding the manufacturing, distribution, importation, exportation and prescribing of controlled substances, the lower numbered schedules imposing greater restrictions than do the higher numbered ones.

There is evidence that combination acetaminophen products significantly contribute to both intentional and unintentional acetaminophen overdoses.[92] Although removing these products from the market would clearly result in a decrease in the cases of hepatic injury, this intervention must be weighed against the role these products play in the pain management for many individuals as the only DEA Schedule III narcotics and the additional risks associated with analgesics used in place of these combinations.

One working group member supports removing Rx acetaminophen combination products from the market. The factors that support the removal of the products include:

- The narcotic and acetaminophen can easily be supplied and taken as single ingredient products. (additional single ingredient narcotic products would need to be developed)
- The contribution of the acetaminophen to the pain relief by combination prescription products is modest at best.[93]
- The products combine a drug, the narcotic, where the maximum dose for an individual patient differs because of tolerance, with acetaminophen, a drug with a significant dose-limiting side effect in patients. If a patient has increasing pain or develops tolerance, titration of the product will increase patient risk for hepatic injury.
- The removal of these products would eliminate them as a source of acetaminophen hepatotoxicity related to taking both a prescription and an OTC acetaminophen product. It is noted that patients may find it particularly difficult to recognize the presence of acetaminophen in their prescription combination product.

The working group, however, rejected this recommendation at this time. The primary factors that support the continued marketing of the combination prescription products include:

- Hydrocodone/acetaminophen combinations products are the most frequently prescribed opioid analgesics. Hydrocodone is a Schedule II drug under the Controlled Substances Act, however, there is a provision that makes hydrocodone in combination with a nonopioid analgesic a Schedule III product under specific conditions.
    - The logical choice to substitute for the combination products would be a single-drug product formulation of hydrocodone, however there are no approved products formulated with hydrocodone alone. The next logical choice would be another Schedule II narcotic analgesic. This group of products includes oral immediate-release oxycodone, hydromorphone, oxymorphone, morphine and meperidine. First, it would be necessary to determine whether there is enough capacity across the pharmaceutical manufacturers to fill the need as these products are currently prescribed with a substantially lower frequency than the

[91] See section Controlled Substances Act sections 201, 202, codified in 21 U.S. 811, 812. See also 42 U.S.C. 242; CDER *Manual of Policies and Procedures*, MAPP 4200.3 (Consulting the Controlled Substance Staff on Abuse Liability, Drug Dependence, Risk Management, and Drug Scheduling)(effective May 8, 2003); CDER *Manual of Policies and Procedures*, MAPP 4200.2 (Forecasting Schedule I and II Substance Drug Needs (effective May 8, 2003).

[92] See Larson (2005), 44% of all acetaminophen cases of acute liver failure involved narcotic/acetaminophen product; 63% of unintentional overdoses involved use of a narcotic/acetaminophen product; 18% of intentional cases involved use of narcotic/acetaminophen product.

[93] See DAARP review p. 2 and 8 -12; There is a suggestion of benefit with combination narcotic / acetaminophen over single ingredient products for acute pain but they have not been adequately studied in chronic pain.

hydrocodone/acetaminophen products. It is important to consider the relative frequency of other adverse events, and in particular with opioids, the relative rates for abuse, misuse and diversion. Oxycodone and hydromorphone are associated with a substantially higher frequency of abuse, misuse and diversion than the hydrocodone/acetaminophen combinations. Having greater inventory of these drugs in the community is likely to result in further increases in the rates of misuse. There are no approved oral immediate-release morphine products currently marketed, but there are unapproved morphine products. Pending approval of marketing applications for immediate-release oral morphine products, additional prescribing of immediate-release morphine may result in an increase in the use of unapproved products. Meperidine has poor oral bioavailability and is not widely prescribed as an oral opioid analgesic.

  - It is also possible that prescribers will consider the use of prescription NSAIDs as a substitute for hydrocodone/acetaminophen products for some patients. While the risk for acetaminophen-induced liver injury is not trivial, the use of NSAIDs, particularly on a chronic basis, is associated with risk for gastrointestinal bleeding, perforation and obstruction, cardiovascular thrombotic events, renal toxicity, anaphylactic reactions, serious skin reactions as well as hepatic toxicity. Overall in the setting of chronic use, there may be little overall reduction in harm from a switch to NSAIDs and possibly an increase.

- All of the currently approved, hydrocodone/acetaminophen products are listed under Schedule III of the CSA. For products listed under Schedule III, prescribers can write prescriptions which allow for up to five refills in a 6-month period. In contrast, refills are not permitted for products listed under Schedule II. These differences can mean substantially increased costs and discomfort for chronic pain patients who are switched to a Schedule II product. As of December 19, 2007, the Drug Enforcement Agency has amended its regulations to allow practitioners to provide individual patients with multiple prescriptions, to be filled sequentially, for the same Schedule II controlled substance, when the multiple prescriptions have the combined effect of allowing a patient to receive over time up to a 90-day supply of that controlled substance.[94] This will, however, still potentially double the number of office visits required for otherwise relatively stable chronic pain patients.
- The current labeling for prescription acetaminophen products does not adequately emphasize the hepatotoxicity risks, but if the labeling were improved, health providers may become more aware of acetaminophen hepatotoxicity and be more likely to caution their patients about not using excessive amounts, thus obviating the need for eliminating the combination products.

There are several factors that, when taken together, could affect the working group's initial recommendation and could warrant revisiting this intervention in the future. First, if the Drug Enforcement Agency (DEA) decides to re-schedule the narcotic combination products to Schedule II, [95] this rescheduling would eliminate the major argument supporting the continued availability of the combination (i.e., ease of prescribing). Second, in conjunction with the first, there would have to be an appropriate single ingredient product available to substitute for the combination products. Third, if public education and improved labeling efforts do not reduce the problem, this elimination option would need to be revisited. It is worth noting that even though the working group recommends that OTC combination products be removed from the market and Rx combinations remain on the market, the two approaches can be well supported. The working group (except for the dissenter) concluded that the benefit of the increased access of a Schedule III over a Schedule II drug outweighs the risk of leaving the combinations on the market, while disadvantages of removing the OTC combination products are not as significant because there are other easily accessible alternatives, and do not outweigh the benefit of removing these combinations.

[94] Issuance of Multiple Prescriptions for Schedule II Controlled Substances. 72 Federal Register 64921 (Nov. 19, 2007).
[95] See Letter from Karen Tandy (U.S. Department of Justice) to Cristina Beato (HHS), dated July 28, 2004.

III. ADDITIONAL IMPLEMENTATION ISSUES

A. Estimate of Impact

The working group was also tasked with providing some estimate of the impact of each intervention on the number of cases of liver toxicity. This can be described in two different ways: 1) qualitatively - describe how the intervention will affect the root cause leading to hepatotoxicity for a specific case, and 2) quantitatively - estimate the percent reduction of the number of events. With the former, we can speculate on the root causes and identify what types of interventions may impact on them. For unintentional overdoses, the problem ultimately is lack of awareness of the patient that he or she is taking an unsafe dose of acetaminophen. This arises because of lack of awareness 1) of the drug being taken and its risks, 2) of the maximum dose that should be taken, 3) of the dose actually being taken, 4) of the presence of acetaminophen in more than one products being taken. The lack of awareness could arise from inadequate labeling, inadequate guidance by practitioners, patient carelessness, and pain inadequately treated by the safe dose. We have proposed steps that in the end should reduce the likelihood of inadvertent overdose. That said, it is hard to know the effect of each.

- We do not have estimates of the number of events that are a result of a specific factor (i.e. root cause). In all cases, there are probably multiple factors that contribute to each event.
- An intervention directed at one factor may not have the impact expected. Other factors may still cause an individual to be at an increased risk. For example, if consumers take two or more medicines containing acetaminophen at the same time, decreasing the tablet size and individual dose will decrease the risk because the total exposure will be decreased, but it will not prevent the risk completely because the total dose could still be hepatotoxic for some people.
- People process and act on information in different ways. People may understand that acetaminophen causes liver injury but ingests two products containing acetaminophen because they are careless about knowing the ingredients in the products. As a consequence, it is important to attack the root causes by more than one intervention.

For many of the interventions proposed in this report, there is little previous experience with similar endeavors that allows us to predict the expected reduction in events. Consequently, we can only guess whether the interventions will have a small, modest or large impact and associate some percentage with those descriptors. It is also not clear that past experience with similar, but not identical, efforts will be a predictor of future outcomes. For example, an aggressive education campaign had a significant impact on decreasing the number of cases of Reye's syndrome associated with aspirin use, fundamentally changed the treatment of children with fever. The FDA and other government agencies embarked on an education campaign[96] in the 1980's that contributed to decreases in the number of cases by greater than 80% even before warnings for Reye's Syndrome were required on aspirin products.[97] But, the message for Reye's Syndrome was simpler (do not give to children with a viral infection) compared to the challenge with acetaminophen (take it but do not take too much). For Reye's Syndrome, all stakeholders conveyed the same message. There were no advertisements emphasizing the safety of aspirin in children. It is different for acetaminophen. Despite some advertisements to encourage the safe use of acetaminophen, there are also many advertisements that describe its safety. They are not incorrect; acetaminophen is safe for the gastrointestinal tract, a non-trivial advantage. Any education campaign will compete with drug advertising. For OTC products, regulated by the FTC, it will be critical for FDA to work with the FTC to assure that it is balanced and informative. There is reason to hope that the proposed education and labeling efforts will have a meaningful impact on unintentional overdose, say 20%.

[96] 50 FR 51400; 53 FR 21633.
[97] 53 FR 21633; The number of cases decreased from 658 in 1980 to 93 in 1985. FDA initiated an education campaign in 1982.

Most of our estimates of the impact of the interventions are pure conjecture, but in one case we may be able to make an educated guess. Decreasing the tablet strength to 325 mg and limiting the individual dose to 650 mg (35% lower than 1000 mg) will reduce the number of cases because people will have a lower exposure if they take the same number tablets that they currently ingest. For example, Larson et al. 2005 studied 662 consecutive patients presenting at 22 tertiary care centers with ALF over a 6-year period. Of these 662 patients, 275 had acetaminophen-induced ALF, of which 131 patients had an *unintentional overdose,* leading to a short term (3-week) fatality rate of 28%, or 36 deaths (0.28 x 131). The median dose of acetaminophen ingested by the group of 131 with an unintentional overdose was 7.5 grams per day. *If the 131 patients had replicated their intake of acetaminophen (same number of doses but fewer mg per dose),* then the median dose for this group would have been 4.875 g (0.65 x 7.5 g). Sixty-five (65) of these patients (those below the median) would have ingested less than 4.875 g. Many, if not most of these 65 might then have avoided ALF, and thus survived. The Larson et al. reference is not clear whether the 28% fatalities (total of 36) are concentrated in patients who ingested above the median dose or are uniform across the 131 patients. However, if the deaths were roughly uniform across the dosing spectrum, then a crude estimate of deaths avoided may be calculated as 18 deaths avoided (28% fatality rate or 0.28 x 65). This assumes that no one ingesting less than 4.875 g would have died. Another estimate of deaths avoided can be arrived at by noting that Larson et al. found that 19 of the 275 patients with acetaminophen-induced ALF reported ingesting less than 4 g per day of acetaminophen (14 of these 19 reported an unintentional overdose). If these 19 *had replicated their intake of acetaminophen (same number of doses but fewer mg per dose),* then they might have ingested only 2.6 g per day (0.65 x 4 g) and most, if not all of them, might have avoided liver failure.

The median dose of acetaminophen ingested by the group with *intentional overdose* leading to ALF was 25 grams. If this group replicated their intake of acetaminophen, then the median dose might have been 16.25 g, which is still a hepatotoxic dose. Too many assumptions are required to estimate deaths averted in this intentional overdose group.

The root causes that lead to liver injury can be broadly categorized under three different headings: 1) people are not aware that acetaminophen can cause liver injury; 2) people make dosing errors so that they take more than the recommended dose or use more than one acetaminophen product at the same time; and 3) some people may be at an increased risk for toxicity based on factors (e.g. alcohol use) unique to them. The following tables illustrate the expected qualitative impact, with some attempt to estimate the size of the effect.

Estimates of Impact of Interventions on Unintentional Acetaminophen Overdose for OTC Products

	Qualitative Impact: Root Causes			Quantitative Impact
OTC Intervention	Not aware of acetaminophen liver toxicity	Dosing error (e.g. two meds at same time, using wrong formulation for age)	At increased risk because of some underlying factor	Impact
Education and labeling and drug name on PDP (identify acetaminophen products)	√	√		< 25% reduction
Decrease total daily dose to 3250 mg and decrease individual dose to 650 mg and tablet strength to 325 mg		√	√	< 25% reduction
One liquid concentration for children		√		100% reduction of cases that are related to dosing errors with more concentrated formulations

Estimates of Impact of Interventions on Unintentional Acetaminophen Overdose for OTC Products

	Qualitative Impact: Root Causes			Quantitative Impact
OTC Intervention	Not aware of acetaminophen liver toxicity	Dosing error (e.g. two meds at same time, using wrong formulation for age)	At increased risk because of some underlying factor	Impact
Eliminate OTC Combination Products		√		< 10% reduction
Require accurate, easily readable dosing cups for liquid formulations		√		Reduce dosing errors related to dosing cups by 25%
Provide dose instruction down to 6 months of age		√		Unclear. Eliminates errors where parent guesses at dose but may increase dose measuring errors.

Estimates of Impact of Interventions on Unintentional Acetaminophen Overdose for Prescription Products

Prescription Intervention	Not aware of liver toxicity associated with acetaminophen	Dosing error (e.g. two meds at same time, using wrong formulation for age)	At increased risk because of some underlying factor	Impact
Education and labeling and drug name on PDP	√	√		< 25% reduction
Decrease total daily dose to 3250 mg, decrease individual dose to 650 mg and tablet strength to 325 mg and unit of use package with warning	√	√	√	< 25% reduction

B. Implementation of Working Group Recommendations for the next 3-6 Months

Once FDA leadership makes decisions about the interventions to pursue, the process for implementation should proceed expeditiously to address this important public health problem. Some of the working group recommendations will take several months or years to complete. Below is a summary of the list of recommendations that the FDA can complete in the next 3 to 6 months:

- Develop and begin to implement the multi-faceted education program
  - Identify the messages to be conveyed and how best to convey them
  - Identify the targets of the educational effort
  - Develop materials that can be used in the campaign
  - Develop outreach programs for health professionals
  - Identify funding sources and amounts to be allocated
- For OTC products, ONP should draft the final rule for labeling internal analgesic products and CDER should clear the rule.
- For OTC products, the limitation on the concentration of pediatric liquid products can be included in an acetaminophen pediatric dosing rule, which CDER should clear.
- For Rx products, take steps to require the container labeling and a liver toxicity warning on the immediate containers.
- For Rx products, create a Boxed warning and Medication Guide and send out uniform supplement request letters
- Begin to assess the effectiveness of interventions
- Begin to identify the databases used to monitor the number of cases of liver injury. These will used to measure the success of the interventions.

- Begin to identify a metric that will accurately assess the extent to which the number of cases of acetaminophen-induced hepatotoxicity is declining after implementation of various interventions. The success of the intervention needs to be reassessed on a pre-defined interval. This interval will depend on what is implemented and the estimated time needed to show an effect.
- Continue to search the literature (and more thorough review of other relevant documents submitted to FDA) to identify additional relevant data.

References from the Medical Literature

Barrett TW, Norton VC. Parental knowledge of different acetaminophen concentrations for Infants and Children. Academ Emerg Med. 2000 Jun 7; 7(6): 718-21.

Bateman DN, Gorman DR, Bain M, Inglis JH, House FR, Murphy D. Legislation restricting paracetamol sales and patterns of self-harm and death from paracetamol-containing preparations in Scotland. Br J Clin Pharmacol. 2006 Nov;62(5):573-81.

Chen L, Schneider S, Wax P. Knowledge about acetaminophen toxicity among emergency department visitors. Vet Human Toxicology. 2002; 44: 370-373.

Daly FS, O'Malley GF, Heard K, Bogdan GM, Dart. Prospective Evaluation of Repeated Supratherapeutic Acetaminophen (Paracetamol) Ingestion. Ann Emerg Med. 2004;44:393 – 398.

Hawkins LC, Edwards JN, Dargan PI. Impact of restricting paracetamol pack sizes on paracetamol poisoning in the United Kingdom: a review of the literature. Drug Saf 2007; 30: 465-79.

Kaufman DW, et. al. Recent patterns of medication use in the ambulatory adult population of the United States: the Slone survey. JAMA. 2002;287(3): 337-44

Lagerlov P, Helseth S, and Holager T. Childhood illnesses and the use of paracetamol (acetaminophen): a qualitative study of parents' management of common childhood illnesses. Fam Pract. 2003 Dec;20(6):717-23.

Larson AM, Polson J, Fontana RJ, Davern TJ, Lalani E, Lee WM et al. Acute Liver Failure Study Group (ALFSG). Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. Hepatology. 2005 Dec;42(6):1364-72.

Lesch MF. Consumer Product Warnings: Research and Recommendations. Handbook of Warnings, Chapter 10. Edited by Michael S. Wogalter. 2006, Lawrence Erlbaum Associates
Li SF, Lacjer B, Crain EF. Acetaminophen and ibuprofen dosing by parents. Pediatr Emerg Care 2000; 16:394-7.

Morgan O et al. Paracetamol (acetaminophen) pack size restrictions and poisoning severity: time trends in enquiries to a UK poisons centre. J Clin Pharm Ther 2007; 32: 449-55.

Nourjah P, Ahmad SR, Karwoski C, Willy M. Estimates of Acetaminophen (Paracetamol)-associated overdoses in the United States. Pharmacoepidemiol Drug Saf. 2006 Jun; 15(6): 398-405.

Schiødt FV, Rochling FA, Casey DL, Lee WM. Acetaminophen toxicity in an urban county hospital. N Engl J Med. 1997 Oct 16;337(16):1112-7.

Shaoul et al. Silent acetaminophen-induced hepatotoxicity in febrile children: does this entity exist? Acta Paediatr 2004; 5: 618-22.

Stumpf JL, Skyles AJ, Alaniz C, Erickson SR. Knowledge of appropriate acetaminophen doses and potential toxicities in an adult clinic population. J Am Pharm Assoc (2003). 2007 Jan-Feb;47(1):35-41.

Tarone RE, Blot WJ, McLaughlin JK. Nonselective nonaspirin nonsteroidal anti-inflammatory drugs and gastrointestinal bleeding: relative and absolute risk estimates from recent epidemiologic studies. Am J Ther 2004 Jan-Feb;11(1):17-25.

Turvill JL, Burroughs AK, Moore KP. Change in occurrence of paracetamol overdose in UK after introduction of blister packs. Lancet. 2000 Jun 10;355(9220):2048-9.

Watkins PB et al. Aminotransferase Elevations in Healthy Adults Receiving 4 Grams of Acetaminophen Daily. JAMA 2006 Jul 5; 296(1); 87-93.

William A. Bower, M.D., Matthew Johns, M.P.H., Harold S. Margolis, M.D., Ian T. Williams, Ph.D.,and Beth P. Bell, M.D. Population-Based Surveillance for Acute Liver Failure . Am J Gastroenterol 2007;102:2459–2463.

Appendices

A. Table: FDA Interventions to Decrease the Occurrence of Acetaminophen Hepatotoxicity: Summary of Recommendations of CDER Working Group
B. Timeline of Significant Events Concerning Acetaminophen Hepatotoxicity
C. Labeling Regulations for OTC Acetaminophen Products Proposed in December of 2006
D. Members of Working Group
E. Office of Surveillance and Epidemiology, *OSE Safety Review (Acetaminophen, Hepatotoxicity, Death)*
F. Office of Nonprescription Products, *Acetaminophen-Induced Hepatotoxicity*
G. Division of Anesthesia, Analgesia, and Rheumatology Products, *Assessment of the Analgesic Efficacy and Hepatotoxicity of Opioid/Acetaminophen Combination Products*
H. Laura Governale Review of acetaminophen use patterns

CONFIDENTIAL
FDA INTERVENTIONS TO DECREASE THE OCCURRENCE OF ACETAMINOPHEN HEPATOTOXICTY
SUMMARY OF RECOMMENDATIONS OF CDER WORKING GROUP

Note: See CDER working group report for additional details. See key at end of Rx tablet for abbreviations.

Over-the-Counter (OTC) Product Recommendations				
Recommendation (also impact on intentional/unintentional overdose)	**Mechanisms to Implement[1]**	**Timeline**	**Most Significant Support for Recommendation**	**Difficulties in Implementation[2]**
1. Enhance public education efforts (primarily intentional, but also possibly unintentional) • Develop concise, clear messages • Pursue partnerships with other governmental agencies, health professionals, industry, consumers, and media • Improve FDA's own educational efforts	Staff from OSE, OND, Office of Training and Communication, and Office of the Commissioner will identify best mechanisms for enhancing public education and will conduct appropriate outreach	Within next 3-6 months, develop educational tools and begin to implement	• Consumers are not aware that acetaminophen overdoses can cause severe liver injury • Supporters of enhanced educational efforts include AASLD, ALF, McNeil Consumer Health Care	• 2004 educational efforts did not significantly reduce problem • Identifying appropriate message about the relative safety of acetaminophen, especially compared to other OTC pain relievers • Likely industry/media resistance to certain messages (e.g., highlighting possibility of severe liver damage with acetaminophen overdose)
2. Improve labeling (unintentional) • Prominently display "acetaminophen" on principal display panel • Highlight/bold acetaminophen in active ingredient list • Warn that taking more than recommended amount may cause severe liver injury	Rulemaking	• Proposed ruled published 12/06 • Within next 3-6 months, CDER should clear final rule • Difficult to predict when final rule will be published, but working group recommends expediting post-CDER clearance	• Improved labeling is effective educational tool • Supporters of improved labeling include American Academy of Family Practice and AASLD	• Difficulty of educating about word "acetaminophen" • Possible industry objections that data do not support label warnings • Likely industry resistance to certain label changes (e.g., referring to possible liver damage as being "serious" and alcohol warnings) • Possible industry resistance because of costs incurred in

[1] OTC products that are NDAs/ANDAs are governed by the mechanisms described in the Prescription (Rx) Product Recommendations Table.
[2] All face funding constraints, competing demands on FDA staff time, burdensome/lengthy rulemaking/clearance process, difficulty in measuring success of interventions, possible legal hurdles, and need for involvement of non-FDA individuals and entities.

CONFIDENTIAL
FDA INTERVENTIONS TO DECREASE THE OCCURRENCE OF ACETAMINOPHEN HEPATOTOXICTY
SUMMARY OF RECOMMENDATIONS OF CDER WORKING GROUP

Over-the-Counter (OTC) Product Recommendations				
Recommendation (also impact on intentional/unintentional overdose)	**Mechanisms to Implement[1]**	**Timeline**	**Most Significant Support for Recommendation**	**Difficulties in Implementation[2]**
• Warn that product should not be used with other acetaminophen products • Warn that consumers should seek prompt medical attention after acetaminophen overdose even without apparent symptoms • Include warnings for people with liver disease • Include warnings for alcohol users • Put acetaminophen liver injury warning on immediate acetaminophen containers		process • Implementing likely to take minimum of 6 months after final rule is published • Labeling that alcohol users should have lower daily dose may require full notice and comment rulemaking		changing labels (although relatively minimal compared to reformulation changes)
3. Limit maximum adult daily dose (unintentional) ▪ Generally limit to 3250 mg ▪ Lower dose further for alcohol users	Rulemaking	Within next 6 months, begin drafting proposed rule; usual rulemaking process will follow	• Acetaminophen has narrow therapeutic-to-toxic window (and Rx and OTC maximum are same), which is troubling because surveys show people routinely take more than recommended doses of OTC pain relievers. • AERS and ALFSG data show doses closer to 4 grams (current daily maximum) present risk to some people • examples of reducing total daily does for Rx products include AZT, Accutane, estrogen dose for	• Limited FDA precedents for reducing OTC maximum daily dose that is safe for most of population because of difficulty to adequately identify at-risk population • Possible industry challenge to evidence of harm at current maximum daily dose • Possible industry challenge to view that sufficiently high percentage of consumer exceed maximum daily recommended acetaminophen dose

CONFIDENTIAL
FDA INTERVENTIONS TO DECREASE THE OCCURRENCE OF ACETAMINOPHEN HEPATOTOXICTY
SUMMARY OF RECOMMENDATIONS OF CDER WORKING GROUP

Over-the-Counter (OTC) Product Recommendations				
Recommendation (also impact on intentional/unintentional overdose)	**Mechanisms to Implement[1]**	**Timeline**	**Most Significant Support for Recommendation**	**Difficulties in Implementation[2]**
			contraception or menopausal symptoms • 4 grams daily over several days showed reversible transaminase elevations • People do not experience negative symptoms for liver toxicity immediately, unlike immediate negative symptoms for NSAIDS overdoses • Supporters of limiting maximum daily adult dose include AASLD and Arnold & Porter	• Possible industry resistance to costs of label change (but low compared to reformulation changes)
4. Limit tablet strength and single adult dose (both intentional and unintentional) • Immediate-release tablet strength to maximum of 325 mg, maximum single adult dose to 650 mg for adult (eliminate 500 mg tablet) • Extended-release modifications according to total daily dose and the dosing increment	Rulemaking for monograph products (except possibly different mechanism for individual tablet strength requirement)	See maximum daily dose timeline above	• Data may not be sufficiently convincing to show that single dose 1000 mg is better than 650 mg for pain relief. • Lower single doses should lead to a lower daily intake (see limiting maximum daily dose above) • Weaker tablet strengths would allow continued practice of 2 pills per dose and lower individual dose • People taking two different acetaminophen products concurrently would have lower total exposure, possibly averting liver injury	• Limited FDA precedents • Adequacy of evidence indicating that tablet strength or single dosage (up to 1000 mg) creates safety concerns (e.g., leads to exceeding maximum daily dose or creating safety concerns for individual dose) as long as maximum daily dose not exceeded • Possible industry assertions that data are adequate to show benefits of 1000 mg over 650mg • Possible industry resistance to costs related to reformulation if necessary and possible loss of revenue from elimination of 500 mg products • Possible consumer resistance to

CONFIDENTIAL
FDA INTERVENTIONS TO DECREASE THE OCCURRENCE OF ACETAMINOPHEN HEPATOTOXICTY
SUMMARY OF RECOMMENDATIONS OF CDER WORKING GROUP

Over-the-Counter (OTC) Product Recommendations				
Recommendation (also impact on intentional/unintentional overdose)	**Mechanisms to Implement[1]**	**Timeline**	**Most Significant Support for Recommendation**	**Difficulties in Implementation[2]**
				elimination of popular 500mg tablet • Possible legal issues about appropriate mechanism for requiring tablet strength change in monograph drug products
5. Limit options in liquid formulation (unintentional) ▪ Limit pediatric liquid formulation to one mid-strength concentration ▪ Require that measuring device be included in each package ▪ Include dosing instructions for children under 2 years	Rulemaking (include in pediatric dosing rule)	Within next 3-6 months, CDER should clear proposed rule	• Acetaminophen overdoses occur because caregivers confuse different formulations of different strengths • Manufacturers have voluntarily changed label and advertising to address confusion, but have not provided evidence that overdosing has been reduced • Acetaminophen overdoses occur because of inaccurate dosing devices • Recent advisory committee recommended similar dosing device standardization for common cold products • Monograph does not include dosing instructions for under 2 years, instead directing that a health professional be consulted. • Supporter of dosing instructions for under 2 years include McNeil	• Limited data on extent to which different liquid formulations, lack of measuring device, and lack of dosing instructions for under 2 result in overdoses • Limited data on effectiveness of public education on pediatric liquid formulations • Possible industry resistance to costs of reformulation and possible loss of revenue if certain products are eliminated • Possible consumer resistance to more limited product choice • Limited FDA precedents and need to be consistent with liquid formulations of other drugs • Eliminating concentrated infant drops might create dosing problems for neonates because of difficulty of ingesting larger volume
6. Eliminate combination products (unintentional)	Rulemaking (complete with maximum daily dose rule above)	See maximum daily dose timeline above	• Consumers may not recognize acetaminophen in combination products	• Possible challenge to retaining Rx combination products while eliminating OTC combination

CONFIDENTIAL
FDA INTERVENTIONS TO DECREASE THE OCCURRENCE OF ACETAMINOPHEN HEPATOTOXICTY
SUMMARY OF RECOMMENDATIONS OF CDER WORKING GROUP

Over-the-Counter (OTC) Product Recommendations				
Recommendation (also impact on intentional/unintentional overdose)	**Mechanisms to Implement[1]**	**Timeline**	**Most Significant Support for Recommendation**	**Difficulties in Implementation[2]**
			• Combination products are solely for convenience	products (but answer is that there is different cost/benefit analysis—see below) • Possible industry and consumer resistance given popularity of OTC combination products • Evidence unclear that OTC combination is significant cause of overdose
7. Identify further research (both intentional and unintentional) • Best way to evaluate success of interventions • Best databases to identify acetaminophen-induced liver injury • Specific products involved in hepatotoxicity • Specific patient populations especially affected and appropriate dosing for these groups • Extent to which efforts to limit acetaminophen liver injury results in additional adverse events by turning to other alternatives • Level of consumer understanding about acetaminophen-induced liver injury	• Current CDER staff more thoroughly review materials submitted to FDA and begin literature searches (including examining experiences in other countries) • CDER Director determines best mechanisms (e.g., interagency working group).	Within next 3-6 months: • Begin to assess effectiveness of interventions • Begin to identify databases used to monitor number of liver injury cases • Begin to identify method to assess effectiveness of each intervention (including reassessment schedule) • Continue literature search and continue review of documents submitted to FDA to identify additional relevant data	• Working group identified these issues are requiring additional data	• Limited financial resources • Time commitment necessary from internal staff with large workloads.

CONFIDENTIAL
FDA INTERVENTIONS TO DECREASE THE OCCURRENCE OF ACETAMINOPHEN HEPATOTOXICTY
SUMMARY OF RECOMMENDATIONS OF CDER WORKING GROUP

Prescription (Rx) Product Recommendations				
Recommendation	**Mechanism to Implement**	**Timeline**	**Additional Support for Recommendation**	**Difficulties in Implementation**
1. Enhance public education efforts (primarily intentional but also unintentional)	Same as OTC			
2.Improve Labeling (unintentional) • Include acetaminophen and liver injury warning on immediate container • Include Medication Guide with information consistent with OTC labeling • Include boxed warning with information consistent with OTC labeling	• For immediate container recommendations, mechanisms still to be determined (e.g., guidance, policy statement, proposed regulations about misbranding) • Uniform supplement request letters for labeling changes to manufacturers	• Within 3-6 months, determine legally appropriate method for immediate container • Create boxed warning, Medication Guide, and send out uniform supplement request letters within next 3-6 months	• Consumers do not always recognize presence of acetaminophen in combination products • Warnings are more effective if users must physically interact with product	• Identifying best mechanism(s) for implementing immediate container requirements • Concerns about Medication Guides in general (June 2007 public hearing) • Possible industry resistance to costs for label changes (although relatively routine compared to reformulation) • Numerous drugs to review labeling supplements
3. Require unit-of-use packaging (both intentional and unintentional)	• Begin with uniform supplement request letters • May require rulemaking to require manufacturers to comply.	• Send out letters within 3-6 months • Timeline for rulemaking contingent on response to letters	• Similar precedents: Zithromax Z-Pac (manufacturer discretion), Fentora, Rescriptor, Accutane • Putting labels on unit-of-use package may help consumers receive message (data supporting increased education when patients must interact with medication)	• Possible industry opposition to added expense and delay in implementation • Possible consumer opposition to added expense, possible difficulty in opening • Data about effectiveness unclear • Numerous drugs to review of many chemistry and labeling
4. Limit maximum adult daily dose (unintentional): same as OTC	See OTC discussion of limiting maximum daily dose and Rx unit-of-use above			

CONFIDENTIAL
FDA INTERVENTIONS TO DECREASE THE OCCURRENCE OF ACETAMINOPHEN HEPATOTOXICTY
SUMMARY OF RECOMMENDATIONS OF CDER WORKING GROUP

Prescription (Rx) Product Recommendations				
Recommendation	**Mechanism to Implement**	**Timeline**	**Additional Support for Recommendation**	**Difficulties in Implementation**
5. Limit maximum tablet strength and single adult daily dose (both intentional and unintentional); same as OTC	See OTC discussion of limiting maximum tablet strength and single adult daily dose and Rx unit-of-use above			
6. Identify research needs (both intentional and unintentional): Same as OTC, and extent to which acetaminophen adds to pain control efficacy of combination	same as OTC	Same as OTC	Working group also identified this issues as requiring additional data in addition to those listed in OTC	same as OTC

Key:
AAFP: American Academy of family Physicians (5/22/07 comments to FR Notice)
AASLD: American Association for the Study of Liver Disease (4/27/07 comments to FR Notice)
ALF: American Liver Foundation (5/24/07 comments to FR Notice)
FR Notice: Notice published in December 26, 2006 *Federal Register* 71 FR 77314-52

Timeline of Significant Events Concerning Acetaminophen Hepatotoxicity

February 2001: At joint FDA/Industry-sponsored conference on drug-induced liver injury, Dr. William Lee presents data from liver transplant centers (from January 1998 to October 2000) showing that acetaminophen poisoning was the most common cause of liver failure, accounting for 38% of the cases (98 of 258); approximately 60% were accidental. This presentation prompts internal FDA discussions to assess the magnitude of the problem of unintentional liver injury associated with acetaminophen.

September 2002: FDA joint Advisory Committee[1] discusses unintentional acetaminophen-related liver injury and NSAIDs-related gastrointestinal bleeding, all in the OTC context. After hearing data presented by FDA, industry, researchers and the public, the Committee recommends: (1) all OTC acetaminophen products should be distinctively labeled (highlighted or bold) on the front panel or principal display panel with the name acetaminophen, (2) all OTC acetaminophen products contain a liver toxicity warning separate from the currently required alcohol warning,[2] (3) FDA and manufacturers should educate consumers and health professionals about the risk of unintentional livery injury from acetaminophen overdoses, and (4) dosing directions for children under 2 years of age should be included on OTC acetaminophen products (as part of general recommendation for dosing instructions for this age group).

January 2003: Article in FDA *Consumer* magazine, warns of possible liver injury from acetaminophen (as well as potential gastrointestinal bleeding from aspirin and other NSAIDs) and states that "FDA is proposing new labeling that will inform consumers of the risk of liver toxicity from products containing acetaminophen."[3]

February 2003: CDER regulatory briefing addresses proposed changes to OTC monograph to address acetaminophen hepatotoxicity and NSAID-related gastrointestinal bleeding.

June 2003: CDER drafts Guidance for Industry *OTC Human Drug Products Containing Analgesic/Antipyretic Active Ingredients –New Warnings and Labeling Changes*, which includes issues of acetaminophen hepatotoxicity; not finalized since OCC did not clear.

January 2004: FDA and partners launch a public education campaign on safe use of OTC pain products, including information about liver damage from acetaminophen use.[4]

January 2004: FDA disseminates Science Background paper, *Safety Concerns Associated with Over-the-Counter Drug Products Containing Analgesic/Antipyretic Active Ingredients for Internal Use*, which includes acetaminophen hepatotoxicity issues. [5]

January 2004: FDA creates page on its Web site, *Safe Use of Over-the-Counter Pain Relievers (analgesic) and Fever Reducers (antipyretics)*, which includes acetaminophen hepatotoxicity issues. [6]

---

[1] Nonprescription Drugs Advisory Committee, Anesthetic and Life Support Drugs Advisory Committee, Arthritis Advisory Committee, Cardiovascular and Renal Drugs Advisory Committee, Drug Safety and Risk Management Advisory Committee, and Gastrointestinal Drugs Advisory Committee. Information about the September 19-20, 2002 meeting is available on FDA's Web Site, *CDER 2002 Meeting Documents*, http://www fda.gov/ohrms/dockets/ac/cder02 htm#NonprescriptionDrugs.

[2] 21 CFR 201.322.

[3] *Use Caution with Pain Relievers*, FDA Consumer Magazine (January-February 2003), available on FDA's Web site at http://www fda.gov/fdac/features/2003/103_pain html.

[4] *Consumer Campaign on Safe Use of OTC Pain Products*, P4-04 (January 22, 2004), available on FDA's Web site at http://www fda.gov/bbs/topics/NEWS/2004/NEW01008.html.

[5] Available on FDA's Web site at http://www fda.gov/cder/drug/analgesics/SciencePaper htm (January 22, 2004).

[6] Available on FDA's Web site at http://www.fda.gov/cder/drug/analgesics/default htm (created January 22, 2004).

January 2004: FDA sends letter to all state boards of pharmacy about acetaminophen hepatotoxicity and NSAID-related gastrointestinal and renal toxicity, asking them to consider requiring labeling on the immediate container of prescription drugs containing acetaminophen that: (1) uses acetaminophen, not APAP, (2) instructs patients to avoid concurrent use of other acetaminophen-containing drugs, (3) instructs patients not to exceed maximum daily recommended acetaminophen dose, and (4) instructs patients to avoid drinking alcohol during prescription use.[7]

May 2004: McNeil (Buc & Beardsley) files with FDA a Federal Data Quality Act (FDQA)(now referred to as Information Quality Act or IQA) complaint and request for correction, claiming that FDA's 2004 public education campaign on safety of various OTC pain products violates IQA because it incorrectly represents that acetaminophen products are less safe than NSAIDs, for example, that: (1) it focuses specifically on liver damage for acetaminophen but says nothing about specific risks for NSAIDs, and (2) acetaminophen ad focuses on risk of overdose, but NSAID ad does not refer to overdose risks.[8]

July 2004: DEA sends letter to HHS asking HHS to provide its scientific and medical evaluation of rescheduling hydrocodone combination products (which include acetaminophen) from Schedule III to Schedule II of the Controlled Substances Act.[9]

August 2004: CDER Director denies McNeil May 2004 IQA request for correction.[10]

October 2004: McNeil appeals CDER August 2004 IQA denial to FDA Commissioner. [11]

March 2005: FDA Commissioner denies McNeil's October 2004 IQA appeal.[12]

December 2005: ALFSG reports that the number of cases of acute liver failure related to acetaminophen has not decreased and in fact may have increased.[13]

June 2006: American Association for the Study of Liver Disease **(**AASLD) writes letter to CDER Director requesting a meeting to discuss FDA past and future steps needed to reduce acetaminophen hepatotoxicity, especially that caused by narcotic/acetaminophen combinations.

July 2006: Study assessing liver functioning finds that 31% to 44% of subjects who ingested 4 grams of acetaminophen per day over 2 weeks had increases in serum alanine aminotransferase of more than 3 times the upper limit of normal. No one in the placebo group had similar elevations. Lab values returned to normal after acetaminophen was discontinued.[14]

---

[7] Letter from Steven Galson to State Boards of Pharmacy, *Acetaminophen Hepatotoxicity and Nonsteroidal Anti-Inflammatory Drug (NSAID)-Related Gastrointestinal and Renal Toxicity* (January 22, 2004), available on FDA's Web site at http://www fda.gov/cder/drug/analgesics/letter htm

[8] The complaint and FDA responses are posted on the HHS Information Quality Web site, I*nformation Requests for Corrections and HHS' Responses, available at* http://www.aspe hhs.gov/infoquality/requests.shtml.

[9] Letter from Karen Tandy, U.S. Drug Enforcement Administration to Cristina Beato, U.S. Department of Health and Human Services (July 28, 2004), in response to citizen petition from Ronald Dougherty to U.S. DEA. (Jan. 4, 1999).

[10] See footnote 8

[11] See footnote 8.

[12] See footnote 8.

[13] Acute Liver Failure Study Group (ALFSG). Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. Hepatology. 2005 Dec;42(6):1364-72. It should be noted that some of this increase may be related to a change in the parameters to identify acetaminophen associated events.

[14] Watkins PB et al. Aminotransferase Elevations in Healthy Adults Receiving 4 Grams of Acetaminophen Daily. JAMA 2006 Jul 5; 296(1); 87-93.

September 2006: FDA receives a citizen petition (2006P-0423) from Pharmacists Planning Service and others requesting that FDA: (1) mandate that all OTC acetaminophen products are clearly labeled "Contains acetaminophen. Do not take with any other Acetaminophen/APAP;" (2) limit the number of 500 mg tablets per OTC package and require that the products be packaged in blister packs; (3) include a Medication Guide for prescription acetaminophen combination products.

December 2006: Sen. Grassley sends letter to FDA Commissioner asking about FDA efforts to promote acetaminophen safety.

December 2006: CDER Director meets with AASLD in response to June 2006 letter.

December 2006: FDA publishes a proposed rule to the labeling and Internal Analgesic OTC drug monograph (specific acetaminophen portions in Appendix C of this Report) that: (1) adds a new liver damage warning to acetaminophen labeling; and (2) requires greater prominence of the name "acetaminophen" on the principal display panel. Federal Register notice also requests data on subpopulations who may not tolerate a total daily dose of 4 grams, the total daily dose for alcohol abusers, and package size and configuration limitations.

January 2007: FDA conducts telephone briefing with Sen. Grassley's staff about FDA efforts to promote acetaminophen safety.

February 2007: OSE submits to CDER Director safety review of acetaminophen (Appendix E of this Report).

March 2007: ONP submits to CDER Director *Acetaminophen-Induced Hepatotoxicity* (Appendix F of this Report).

March 2007: DAARP submits to CDER Director *Assessment of the Analgesic Efficacy and Hepatotoxicity of Opioid/Acetaminophen Combination Products* (Appendix G of this Report).

March 2007: CDER director appoints CDER acetaminophen hepatotoxicity working group to make recommendations for FDA interventions to reduce acetaminophen hepatotoxicity.

March 2007: DAARP sends CSS a consult on hydrocodone/acetaminophen combination products (e.g., Vicodin, Zydone, Lortab) in response to July 2004 DEA request for scientific and medical evaluation and scheduling recommendation concerning hydrocodone combination products.[15]

March 2007: Sen. Grassley sends letter to FDA Commissioner asking for follow-up to January 2007 briefing.

April 2007: FDA staff meets with Sen. Grassley's staff to follow up on March 2007 letter.

April 2007: FDA holds Type C Meeting with McNeil on educational initiatives on OTC products, including acetaminophen.

August 2007: USP seeks FDA input on efforts to clarify that acetaminophen is also referred to as paracetamol.

---

[15] Jin Chen (DAARP), Memorandum to Corinne Moody (CSS), *Response to Request for Consultation: CSS Consult on the Role of Hydrocodone/Acetaminophen Combination Products in the Therapeutic Armamentarium Related to: AMDA 88-058 (Vicodin), ANDA 40-288 (Zydone), ANDA 40-100 (Lortab), Etc.*(March 15, 2007).

Proposed OTC Labeling Regulations Specifically for Acetaminophen Products[1]

21 CFR 201.325(a)(1)(i) ***Principal display panel.*** The presence of "acetaminophen" in the product must be prominently stated on the principal display panel (PDP), as defined in § 201.60.

21 CFR 201.325(a)(1)(ii) ***Statement of identity.*** The statement of identity appears in accord with §§ 201.61, 299.4, and 343.50(a) of this chapter. The ingredient name acetaminophen must appear highlighted (e.g., fluorescent or color contrast) or in bold type, be in lines generally parallel to the base on which the package rests as it is designed to be displayed, and be in one of the following sizes, whichever is greater: (1) At least one-quarter as large as the size of the most prominent printed matter on the PDP, or (2) at least as large as the size of the ''Drug Facts'' title, as required in § 201.66(d)(2). The presence of acetaminophen must appear as part of the established name of the drug, as defined in § 299.4 of this chapter. Combination products containing acetaminophen and a nonanalgesic ingredient(s) (e.g., cough-cold) must include the name "acetaminophen" and the name(s) of the other active ingredient(s) in the product on the PDP in accord with this paragraph. Only the name "acetaminophen" must appear highlighted or in bold type, and in a prominent print size, as described in this paragraph.

21 CFR 201.325(a)(1)(iii) ***For products labeled for adults only. Warnings.*** The labeling of the product states the following warnings under the heading "Warnings":

(A) "Liver warning [heading in bold type]: This product contains acetaminophen. Severe liver damage may occur if you take [bullet] more than [insert maximum number of daily dosage units] in 24 hours [bullet] with other drugs containing acetaminophen [bullet] 3 or more alcoholic drinks every day while using this product". This "Liver warning" must be the first warning under the "Warnings" heading. For products that contain both acetaminophen and aspirin, this "Liver warning" must appear after the "Reye's syndrome" and "Allergy alert" warnings in § 201.66(c)(5)(ii)(A) and (c)(5)(ii)(B) and before the "Stomach bleeding warning'' in paragraph (a)(2)(iii)(A) of this section.

(B) "Do not use [heading in bold type] with any other drug containing acetaminophen (prescription or nonprescription). Ask a doctor or pharmacist before using with other drugs if you are not sure."

(C) "Ask a doctor before use if you have [heading in bold type] liver disease".

21 CFR 201.325(a)(1)(iv) ***For products labeled only for children under 12 years of age.***

(A) *Warnings*. The labeling of the product states the following warnings under the heading "Warnings":

(*1*) "Liver warning [heading in bold type]: This product contains acetaminophen. Severe liver damage may occur if the child takes [bullet] more than 5 doses in 24 hours [bullet] with other drugs containing acetaminophen". This "Liver warning" must be the first warning under the "Warnings" heading.

(*2*) "Do not use [heading in bold type] with any other drug containing acetaminophen (prescription or nonprescription). Ask a doctor or pharmacist before using with other drugs if you are not sure."

(*3*) "Ask a doctor before use if the child has [heading in bold type] liver disease".

(B) *Directions*. The labeling of the product contains the following information under the heading "Directions": "this product does not contain directions or warnings for adult use'' [in bold type].

---

[1] 71 FR 77314-52 (December 26, 2006). Other portions of the proposed regulations also apply to OTC products containing acetaminophen, but are not limited to those products and apply to any OTC product that is governed by the Tentative Final Monograph for Internal Analgesic, Antipyretic, and Antirheumatic Drug Products.

21 CFR 201.325(a)(1)(v) ***For products labeled for adults and children under 12 years of age*****.** *Warnings*. The labeling of the product states all of the warnings in paragraphs (a)(1)(iii)(A), (a)(1)(iii)(B), and (a)(1)(iii)(C) of this section with the following modifications:

(A) The Liver warning states "Liver warning [heading in bold type]: This product contains acetaminophen. Severe liver damage may occur if [bullet] adult takes more than [insert maximum number of daily dosage units] in 24 hours [bullet] child takes more than 5 doses in 24 hours [bullet] taken with other drugs containing acetaminophen [bullet] adult has 3 or more alcoholic drinks everyday while using this product."

(B) "Ask a doctor before use if the user [heading in bold type] has liver disease."

21 CFR 343.50(c)(1)(iii) ***For products containing acetaminophen identified in § 343.10(a)*****.** The labeling states the warnings in § 201.325(a)(1)(iii)(A), (a)(1)(iii)(B), and (a)(1)(iii)(C) and the following statement must follow the general warning identified in § 330.1(g) of this chapter: "Prompt medical attention is critical for adults as well as for children even if you do not notice any signs or symptoms."

21 CFR 343.50(c)(2)(iii) ***For products containing acetaminophen identified in § 343.10(a)*****.** The labeling states the warnings in § 201.325(a)(1)(iv)(A)(1), (a)(1)(iv)(A)(2), and (a)(1)(iv)(A)(3) and the following statement must follow the general warning identified in § 330.1(g) of this chapter: "Prompt medical attention is critical even if you do not notice any signs or symptoms."

21 CFR 343.50(c)(3)(iii) ***For products containing acetaminophen identified in § 343.10(a)*****.** The labeling states the warnings in § 201.325(a)(1)(v) of this chapter. The warning in § 201.325 (a)(1)(v)(B) is modified to read: "Ask a doctor before use if the user [heading in bold type] [bullet] has liver disease [bullet] is a child with pain of arthritis". The following statement must follow the general warning identified in § 330.1(g) of this chapter: "Prompt medical attention is critical for adults as well as for children even if you do not notice any signs or symptoms."

Members of CDER Working Group on Reducing Acetaminophen Hepatotoxicity

The members of the working group include members from various offices within the Center for Drug Evaluation and Research as listed in the following table.

Office/Division Represented	Members
Office of Nonprescription Products	Charles Ganley Susan Johnson Steven Osborne
Office of Regulatory Policy	Elena Cohen
Office of Surveillance and Epidemiology	Mark Avigan Gerald Dal Pan Mary Willy
Division of Anesthesia, Analgesia, and Rheumatology Products	Sharon Hertz Bob Rappaport Rigoberto Roca
Controlled Substances Staff	Silvia Calderon
Office of Medical Policy	Robert Temple

Walt Ellenberg Project Manager

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 5, 2007

FROM: Yoo Jung Chang, Pharm.D., Safety Evaluator
Parivash Nourjah, Ph.D., Epidemiologist
Syed Rizwanuddin Ahmad, M.D., M.P.H., Medical Epidemiologist
Mary Willy, Ph.D., Epidemiologist
Division of Drug Risk Evaluation, HFD-430

THROUGH: Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation, HFD-430

TO: Charles Ganley, M.D., Director
Office of Non-Prescription Drug Products, HFD- 560
Robert Rappaport, M.D., Director
Division of Anesthesia, Analgesia, and Rheumatology, HFD-170

SUBJECT: OSE Safety Review
Drug: acetaminophen
Reaction: hepatotoxicity, overdose, and death

PID #: D060349
RCM #: 2006-23

****This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.****

1. EXECUTIVE SUMMARY

Acetaminophen (APAP) overdose continues to be the leading cause of acute liver failure (ALF) in the U.S. and involves the misuse/abuse of OTC formulations (in all age groups) as well as prescription products that contain both acetaminophen and opiates. Larson et al reported that the proportion of all acute liver failure cases attributed to acetaminophen overdose identified by investigators of the Acute Liver Failure Study Group (a consortium of liver transplant centers that conduct ongoing studies related to acute liver failure) has increased from 26% in 1998 to 51% in 2003. During this time period 48% of the acetaminophen overdoses were unintentional, with 63% of the unintentional overdoses resulting from narcotic-containing drugs.

In September 2002, the Nonprescription Drugs Advisory Committee meeting was held to address this public health issue; the primary area for discussion was the risk of acetaminophen induced hepatotoxicity, factors that might contribute to hepatotoxicity, and additional measures to increase prescriber/patient understanding of the potential risk from the use of acetaminophen products. As a follow-up to this meeting, the Agency launched a consumer education effort related to the safe use of this product in 2004. A review of the current Adverse Events Reporting System (AERS) data and national databases {i.e.) and Toxic Exposure Surveillance System (TESS)} suggest that the 2004 educational campaign did not lead to any significant changes in the number of acetaminophen-related events or their severity, although there is insufficient data to prove the lack of any effect. Major findings are as follows:

AERS DATA - CRUDE COUNTS

- Acetaminophen is currently the number one marketed drug associated with acute liver failure and serious and life-threatening hepatotoxicity in the AERS database.
- According to AERS crude counts, the number of all adverse events, deaths, liver toxicity, overdose, and suicide in association with acetaminophen has trended upwards since the late 1990's to the mid 2000's.
- The crude number of acute liver failure reports submitted to AERS more than quadrupled in the past decade from 89 in 1995 to 404 in 2005. The number of liver toxicity reports with death as an outcome increased more than 7 fold over the same time period from 34 in 1995 to 242 in 2005.
- The crude number of acute liver failure reports and deaths, overdose, and suicide in AERS continued to increase from 2004 to 2005 despite the educational effort launched by the Agency in January 2004.
- Acetaminophen has the highest number of domestic reports of death from all causes compared to ibuprofen, ketoprofen, naproxen, and aspirin, and continues to increase at the highest rate.
- Data mining analysis is consistent with AERS data in that acetaminophen has high association scores (EBGM>8) with various MedDRA PTs related to clinically significant hepatic events (hepatorenal failure, hepatic necrosis, hepatic failure, hepatic encephalopathy, coma hepatic, liver transplant, and hepatotoxicity).

AERS REVIEW OF 100 DEATH CASES FROM 2005

- Approximately half (53%) of the cases were likely or probably associated with acetaminophen toxicity based on hepatic involvement or high acetaminophen levels.
- Suicide and intentional misuse accounted for 82% of the cases.
- Approximately one-quarter (26%) of the deaths were likely due to the narcotic component of a prescription acetaminophen/narcotic combination product. Of these deaths, 58% (11/19) were intentional overdoses (suicides) while 26% (5/19) were unintentional fatalities.

- The most reported category of acetaminophen containing products was the prescription acetaminophen combination with narcotic (59%) followed by the over-the-counter (OTC) single ingredient acetaminophen (33%).
- More than half of the acetaminophen containing products in the prescription acetaminophen combination with narcotic category (65%) and OTC single ingredient acetaminophen category (70%) involved intentional overdoses (suicide) while unintentional fatalities were much lower (prescription acetaminophen combination with narcotic 21% and OTC single ingredient acetaminophen 22%).
- The majority of cases (90%) reported use of only one acetaminophen containing product.

EPIDEMIOLOGIC DATA

- As a risk management intervention, the introduction of blister packs in the UK is one that has been studied and reported by a number of investigators. Analyses of the effectiveness of this strategy have yielded different findings.(Appendix 3). Although many of the studies from the UK suggest there might be some benefit from restriction of the number of tablets and blister-packs, other studies did not find a significant reduction in admissions or days of hospital stay and one study actually reported an increase in overdoses. The concern that people with overdoses would switch to other non-acetaminophen drugs was not supported by some but was supported by others.
- Calls to Poison Control centers have increased for single ingredient, OTC combination, and prescription acetaminophen-containing products.
- The numbers of calls resulting in fatality have not changed drastically when analyzed by product category; nonetheless, when all acetaminophen products are combined the numbers have decreased from 214 in 2003 to 188 in 2005.
- Calls to Poison Control centers show a difference in the proportion of people with intentional versus unintentional overdose between OTC and prescription acetaminophen products; 66% of single ingredient products calls and 52% of OTC combination products calls were unintentional, while 34% of prescription acetaminophen products calls were unintentional.

Outdated material has been redacted and updated information will be presented at the advisory committee meeting.

DRUG USE DATA

- Use, as measured by units sold, for prescription and OTC acetaminophen containing products grew by 17% from year 2001 to 2005.
- The sale of OTC acetaminophen containing products grew by 6% from year 2001 to 2005. The majority of OTC acetaminophen containing products are found in combination with other active ingredients (56% combination acetaminophen containing products versus 44% single-ingredient acetaminophen products). The sale of OTC single-ingredient acetaminophen drug products decreased by approximately 1.5% while combination acetaminophen OTC products increased by approximately 13% from year 2001 to year 2005.
- The sale of prescription acetaminophen containing products realized a growth of 38% from year 2001 to 2005. Hydrocodone/APAP products accounted for over 57% of all dispensed prescriptions in this market, and it has been the number one dispensed prescription product in the entire market of retail dispensed prescriptions since 1997. In 2005, the codeine and combination non-injectable *class* (USC5 02232, which includes hydrocodone/acetaminophen, oxycodone/acetaminophen, codeine/acetaminophen, etc.) was the most dispensed class of acetaminophen containing products for all age groups except for the age 0-5 year band which had the highest number of dispensed prescriptions for the acetaminophen class (USC5 02120) of products. The extent of co-use of OTC and prescription acetaminophen products was not measurable in this analysis due to limitations in data collection.
- According to a survey of approximately 3,100 office-based physician practices in the U.S., the top 5 indications for use of the codeine and combination non-injectable acetaminophen containing products (which includes hydrocodone/acetaminophen, oxycodone/acetaminophen, codeine/acetaminophen, etc.) in 2005 were unspecified disorders of the back (4.5%), follow-up examination (3.6%), mononeuritis of the upper limb (2.7%), radius and ulna fracture (2.7%), and sprain of ankle and foot (2.6%). The top 3 diagnoses with the longest mean days of therapy for hydrocodone/acetaminophen product use in 2005 were osteoarthritis (37 days), arthropathies (33 days), and unspecified disorders of the back (27 days). This data shows that acetaminophen-narcotic combinations are used widely for various pain management including chronic pain, and the longest mean days of therapy for hydrocodone/acetaminophen use was for chronic conditions such as back and joint pain.

RECOMMENDATIONS

In addition to the above findings, an extensive review of risk minimization efforts in the U.K. and, to some extent, in other countries suggests that certain strategies may decrease the number of reports of morbidity and mortality associated with acetaminophen misuse. The following recommendations are being proposed for consideration. These have been ranked in the order of ease with which they can be implemented.

1. Expanded Educational Efforts:

In January 2004, FDA launched a consumer educational campaign to promote safe use of acetaminophen which doesn't appear to have had any major impact in reducing the problems associated with acetaminophen as evidenced by the current review. In December 2006, FDA proposed to amend labeling regulations for over-the-counter acetaminophen products which will require new warnings to highlight the potential for hepatotoxicity particularly in association with the usage of high dose acetaminophen, when multiple acetaminophen products are taken concomitantly, and in the setting of moderate alcohol intake. While the proposed rule addresses issues with labeling of OTC products containing acetaminophen, it does not include educational efforts. *These proposed amendments should be accompanied by expanded educational efforts directed to both the consumers and the health care professionals to enhance and promote safe use of acetaminophen products. Examples would be public service announcements in the newspapers, popular magazines, as well as doctor office and pharmacy flyers and posters, and radio and television advertisements.*

2. Reduction of Pack Size/Blister Pack:

A number of countries in Europe (United Kingdom, Germany, France, Sweden, Switzerland, and Belgium) have restricted the total number of acetaminophen tablets that can be sold over-the-counter to prevent acetaminophen misuse. Overall, it is difficult to make a summary conclusion about the overall effectiveness of this approach given the different study limitations, but there is some suggestion that restriction of the number of tablets and blister-packs may be beneficial. Many of the studies from the UK (and other countries) suggest there might be some benefit from restriction of the number of tablets and blister-packs, with a 21 % reduction in deaths, a 30-50% reduction in severe hepatotoxicity, a 31 % reduction in admissions and an 11 % reduction in non-fatal overdoses. On the other hand, some other studies did not find a significant reduction in admissions or days of hospital stay and one study reported an increase in overdoses. *Taken together, given that there is some suggestion that there may be benefit to this intervention, reducing the pack size of acetaminophen products and availability of blister package should be considered.*

3. Reduction in Maximum Recommended Dosage/Maximum Strength:

Evidence suggests that there is a relatively narrow margin between the maximum recommended daily dose of 4 grams of acetaminophen and doses that are associated with hepatotoxicity. Bearing in mind that the minimum toxic dose of acetaminophen has been as low as 6 g per day in some cases, consideration should be given to reduce the maximum daily dosage from 4 grams to 3 grams (QID to TID) for acute pain control, and also to reduce the maximum tablet and capsule strength of acetaminophen to 325 mg. According to the Proposed Rule for 21 CFR Parts 201 to 343 in the Federal Register of December 26, 2006, there is AERS data to raise concern that a maximum daily dose of 4 grams may not be safe for at risk subpopulations, but the data is limited on which subpopulations are at risk and what is considered a safe dose. *Therefore, consideration should be given to decrease the currently labeled maximum daily dose of 4 grams because this implies that it is generally recognized as safe and effective for use in the general population.*

In addition, reducing the maximum tablet and capsule strength of acetaminophen to 325mg should be considered in light of the current safety issue with acetaminophen toxicity and liver failure. According to the Proposed Rule for 21 CFR Parts 201 to 343 in the Federal Register of December 26, 2006, the rationale for marketing 500 mg tablets in 1973 was that the higher strength would have greater analgesic efficacy, and two of four double-blind, placebo-controlled post partum pain studies demonstrated that two 500 mg capsules (1000 mg) was significantly more effective than a single dose of two 325 mg tablets (650 mg). Further analysis to determine whether these studies would stand up to the current standard for clinical trials and risk versus benefit analysis of today should be undertaken, bearing in mind the safety issues that have come to light.

4. Unbundle Prescription Combination Products:

Keeping in view that prescription narcotic combination acetaminophen products comprise a significant proportion of patients who develop drug-induced acute liver failure, with Larson et al finding that 53% of their study patients ingested prescription acetaminophen/narcotic compounds and 79% of those with prescription acetaminophen/narcotic overdoses were unintentional, *consideration should be given to unbundling these combination products.* Removing acetaminophen from acetaminophen/opiate combination products is expected to decrease the number of unintentional overdoses and unintended outcomes that result from acetaminophen toxicity. Opiate and acetaminophen combination products are widely prescribed, and the hydrocodone/acetaminophen combination product is the number one dispensed prescription product, which is troubling since the opiate component of the drug has a high addictive and tolerance profile requiring increasing doses of the opiate to maintain pain control, thereby inadvertently increasing acetaminophen and causing a hitchhiker effect. By unbundling these narcotic combination products, prescribers will have to prescribe single ingredient opiate and/or single ingredient acetaminophen products separately with instructions to take them together, if appropriate. The patient may be inconvenienced by

having to take two or more tablets versus one and the prescribing patterns of providers may potentially shift to other drugs causing an increase in unintended adverse events from other products. These potential effects do not change the fact that the benefit of reducing acetaminophen overdose and toxicity in the population overall will have a positive public health impact. Most narcotic and acetaminophen combinations are schedule 3 and unbundling it will result in a single ingredient narcotic which is currently schedule 2; however, this should not be an unreasonable barrier for prescribers and patients in having access to each component of these products.

TABLE OF CONTENTS

2. BACKGROUND

2.1 Introduction

Acetaminophen is a non-opiate, non-salicylate analgesic and antipyretic. It produces analgesia by elevation of the pain threshold and antipyresis through action on the hypothalamic heat-regulating center. In the United States, acetaminophen is available as a single ingredient and in combination with one or more drugs (i.e. chlorpheniramine, dextromethorphan, diphenhydramine, doxylamine, guaifenesin, pamabrom, pseudoephedrine, aspirin, caffeine, propoxyphene, hydrocodone, phenylephrine, pyrilamine, phenytoloxamine, oxycodone, codeine, butalbital, isometheptene, dichloralphenazone, and tramadol). Depending on the drug combination, it is available as either prescription or over-the-counter (OTC). Single ingredient acetaminophen is available only as OTC.

2.2 2002 Advisory Committee and Educational Campaign

On September 19, 2002, the Nonprescription Drugs Advisory Committee met to discuss safety issues related to the use of acetaminophen. The meeting also included members from other advisory committees: Anesthetic and Life Support Drugs Advisory Committee, Arthritis Advisory Committee, Cardiovascular and Renal Drugs Advisory Committee, Drug Safety and Risk Management Advisory Committee, and Gastrointestinal Drugs Advisory Committee. The primary area for discussion was on the potential hepatotoxicity related to the use of acetaminophen in both over-the-counter and prescription products. The committee was asked to discuss factors that might contribute to hepatotoxicity and additional measures to increase prescriber and patients understanding about the potential risk from acetaminophen products. The committee recommended certain changes in labeling and a special education effort.

In January 2004 the Agency launched a consumer education effort related to the safe use of acetaminophen (see http://www.fda.gov/cder/drug/analgesics). The campaign included a special brochure (The best way to take your over-the-counter pain reliever?) that was distributed in pharmacies and by health care providers, a reprint of "Use Caution With Pain Relievers", that was distributed at national healthcare conferences and available for reprinting (reprinted from the FDA Consumer magazine), and two print public service advertisements that were sent to approximately 100 magazines.

2.3 Proposed Rule

In December 2006, the Agency proposed to amend the labeling regulations to over-the-counter (OTC) Internal Analgesic, Antipyretic and Antirheumatic (IAAA) drug products to add important safety information. For products containing acetaminophen, the following labeling changes have been proposed:

- To require that the ingredient acetaminophen be prominently identified on the product's principal display panel (PDP) of the immediate container, and the outer carton (if applicable).
- To require new warnings which would highlight the potential for liver toxicity and to warn consumers against using more than the recommended dose of acetaminophen; using more than one product (over-the-counter or prescription) containing acetaminophen, and taking acetaminophen with moderate amounts of alcohol.

This proposed rule is applicable only to OTC drug products and not to prescription products of IAAA ingredients or acetaminophen. It does not address packaging in blister packs, reducing package size, or reducing the maximum tablet/capsule strength, as mentioned in the recommendations section of this consult.

2.4 Summary of Past AERS Hepatotoxicity Consult

A previous OSE review of acetaminophen and hepatotoxicity was conducted by Claudia Karwoski in August 2002 (OSE, formerly ODS).[1] The review analyzed AERS cases received by the agency from 1998 to July 2001. After cases of suicide were excluded from the review; 307 US cases remained for analysis, of which 282 cases involved adults and patients greater than 12 years of age, and 25 cases involved pediatric patients. For both the pediatric and adult cases, 60% were categorized with severe life threatening liver injury and liver failure. Fatalities occurred in approximately 40% of all patients.

Findings from the adults and patients greater than 12 years of age (n=282):

- An unspecified acetaminophen product was most frequently implicated (38%), followed by prescription combination products with narcotics (33%), then OTC single ingredient acetaminophen products (21%).
- Approximately 25% took more than one acetaminophen containing product.
- Of the cases involving the use of two acetaminophen containing products, the combined use of a prescription combination product with narcotic and an unspecified acetaminophen product (48%) or single ingredient acetaminophen product (21%) occurred most frequently.

---

1 Karwoski C, ODS Safety Review – Acetaminophen, Briefing Document: Acetaminophen Containing Products and Hepatotoxicity, August 2, 2002

- In cases where the dose was reported, the mean and median daily dose was 6.5 and 5 gm/day, respectively. The median daily dose increased with the severity of hepatic injury. Overall, 41% suggested that >4 grams per day was ingested, 22% suggested that </=4 grams per day was ingested, and 37% did not provide any dosing information.
- Potential contributing factors or confounders were noted in 62% of the cases, including ethanol use (41%), underlying liver disease (25%), and the use of potentially hepatotoxic co-suspect medication (22%).

Findings from the pediatric cases (n=25):

- Single ingredient acetaminophen (68%) or an unspecified acetaminophen product (44%) was most commonly implicated.
- The most frequently reported product was an acetaminophen concentrated liquid formulation (100mg/ml).
- Most (88%) were receiving only one OTC single ingredient acetaminophen containing product.
- 84% of the cases involved medication errors (improper measuring device, misinterpretation of labeling dosing guidelines or instructions provided by a health care provider, or confusion over differing acetaminophen product concentrations).

Overall summary of review:

- 60% were categorized with severe life threatening liver injury and liver failure.
- Fatalities occurred in approximately 40% of patients.
- In adult cases of hepatotoxicity, the prescription acetaminophen/narcotic combination products were used more frequently than OTC single ingredient acetaminophen products, whereas in children, most cases involved only one OTC single ingredient acetaminophen containing product.
- Approximately 25% of adult hepatotoxicity cases reported the use of more than one acetaminophen containing product, whereas in pediatric cases, most cases reported the use of only one acetaminophen product.
- Among unintentional exposures, the use of higher than recommended doses of acetaminophen occurred more often than the use of recommended doses or less for both adult and pediatric cases.
- For pediatric cases, higher than recommended doses appeared to occur mostly as a result of caregiver misunderstanding or product confusion.

3. DRUG LABELING

Sections of the OTC acetaminophen drug labeling provide relevant information pertaining to overdose, hepatotoxicity, alcohol consumption, and the use of other products containing acetaminophen:

Overdosage:
In acetaminophen overdosage: dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams and fatalities with less than 15 grams.

Alcohol warning:
If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take acetaminophen or other pain relievers/fever reducers. Acetaminophen may cause liver damage.

Use of concomitant product containing acetaminophen:
Do not use

- with any other product containing acetaminophen

4. DRUG USE SUMMARY

A recent review of OTC and prescription combination acetaminophen drug use was conducted by Laura Governale from the Division of Surveillance, Research, and Communication Support (DSRCS) [2], and a summary of the findings are described in the following paragraphs. The use, as measured by units sold, for prescription and OTC acetaminophen containing products grew by 17% from year 2001 to 2005. The sale of OTC acetaminophen products grew by 6% from year 2001 to 2005, while the sale of prescription acetaminophen containing products increased by 38%.

The majority of OTC acetaminophen products are found in combination with other active ingredients (56% combination acetaminophen products versus 44% single-ingredient acetaminophen products). The sale of OTC single-ingredient acetaminophen drug products decreased by approximately 1.5% while combination acetaminophen products increased by approximately 13% from year 2001 to year 2005.

For OTC single-ingredient acetaminophen products, the systemic oral solid regular dosage form accounted for 60% of the market whereas the oral solid long-acting dosage form accounted for 12% of the market during year 2005. The systemic oral solid long-acting dosage form increased by three-fold from year 2001 to year 2005.

---

2 Governale L, DSRCS/OSE Drug Use Data – OTC and Prescription combination APAP Use, November 30, 2006

For OTC combination acetaminophen products, the systemic oral liquid dosage form increased by 34% from year 2001 to year 2005. The most common active ingredient found in combination with acetaminophen was pseudoephedrine.

For prescription acetaminophen containing products, hydrocodone/APAP products accounted for over 57% of all dispensed prescriptions in this market, and has been the number one dispensed prescription product in the entire market of retail dispensed prescriptions since 1997. During year 2005, the codeine and combination non-injectable *class* (USC5 02232, which includes hydrocodone/acetaminophen, oxycodone/acetaminophen, codeine/acetaminophen, etc.) was the most dispensed class of acetaminophen containing products for all age groups except for the age 0-5 year band which had the highest number of dispensed prescriptions for the acetaminophen class (USC5 02120) of products. The extent of co-use of OTC and prescription acetaminophen products may be underestimated in this analysis due to limitations in data collection.

According to a survey of approximately 3,100 office-based physician practices in the U.S., the top 5 indications for use of the codeine and combination non-injectable acetaminophen containing products (which includes hydrocodone/acetaminophen, oxycodone/acetaminophen, codeine/acetaminophen, etc.) in 2005 were unspecified disorders of the back (4.5%), follow-up examination (3.6%), mononeuritis of the upper limb (2.7%), radius and ulna fracture (2.7%), and sprain of ankle and foot (2.6%). The top 3 diagnoses with the longest mean days of therapy for hydrocodone/acetaminophen product use in 2005 were osteoarthritis (37 days), arthropathies (33 days), and unspecified disorders of the back (27 days).[3] This data shows that acetaminophen-narcotic combinations are used widely for various pain management including chronic pain, and the longest mean days of therapy for hydrocodone/acetaminophen use was for chronic conditions such as back and joint pain.

3 Governale L, DSRCS/OSE Drug Use Data – Mean therapy days for hydrocodone/acetaminophen and other acetaminophen containing products, January 4, 2007

5. SUMMARY OF AERS DATA

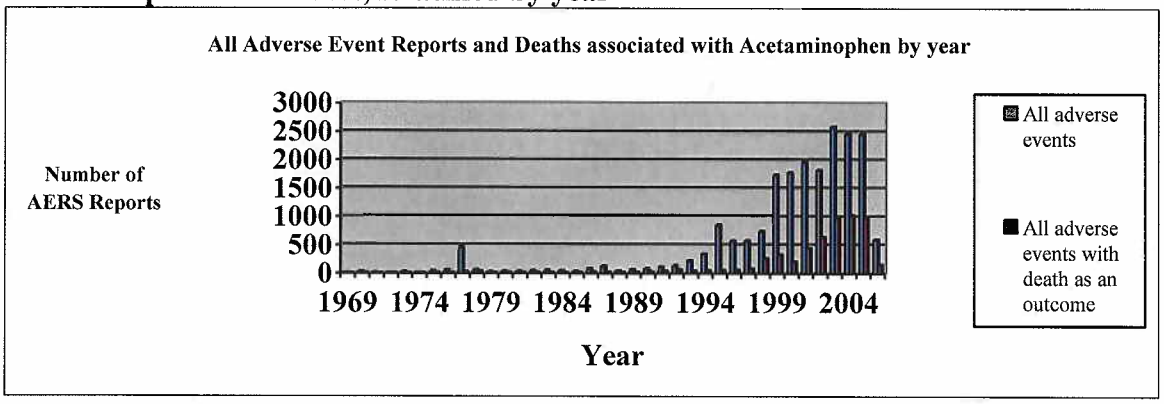
5.1 SUMMARY OF CRUDE AERS DATA

5.1.1 All Adverse Events with Acetaminophen

As of August 17, 2006, a total of 25,237 serious and non-serious adverse event reports for acetaminophen were identified in the AERS database, of which 20,252 were domestic reports. Of the 20,252 domestic reports, 28% (5,581) had a death outcome. It is important to note that these reports cited the use of single ingredient and/or combination acetaminophen products. These numbers are crude report counts and may include duplicates. Given the large number of reports, individual reviews were not performed to determine an association between the reported event and the use of acetaminophen; these reports may contain concomitant use of other medications.

Figure 1 below depicts the number of all domestic adverse event reports and deaths in AERS associated with acetaminophen, stratified by year.

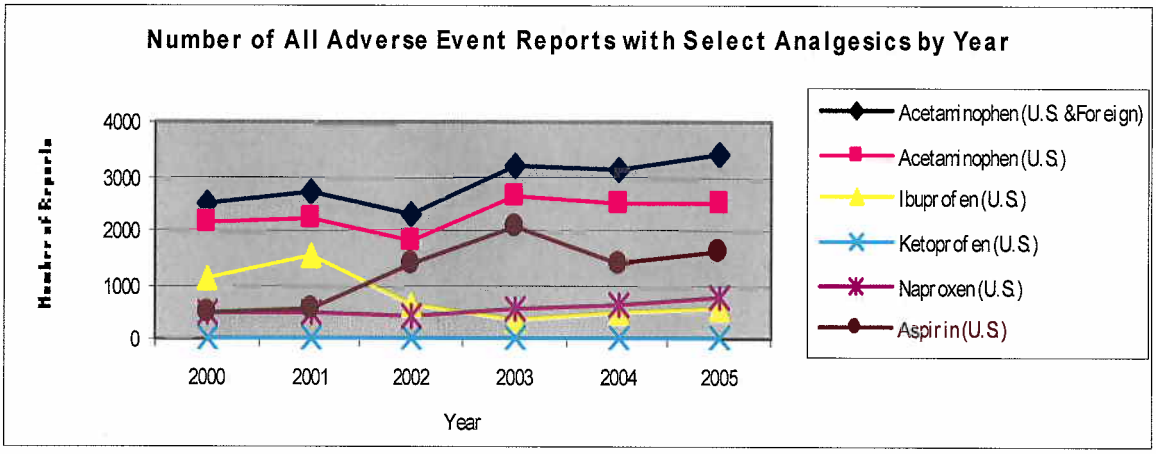
Figure 1. Crude AERS count of all adverse event reports and deaths for acetaminophen in the U.S., stratified by year



Adverse event reports and deaths associated with acetaminophen have trended upwards in the U.S. from the 1990's to the mid 2000's. The number of all adverse event reports in the U.S. (20,252) has more than quadrupled in the past 9 years from 572 in 1996 to 2,458 in 2005. The number of death reports (5,581) has quadrupled in the past 5 years from 201 in 2000 to 980 in 2005.

Figure 2 below compares the number of all adverse events in AERS associated with acetaminophen to several other analgesics, stratified by year.[4]

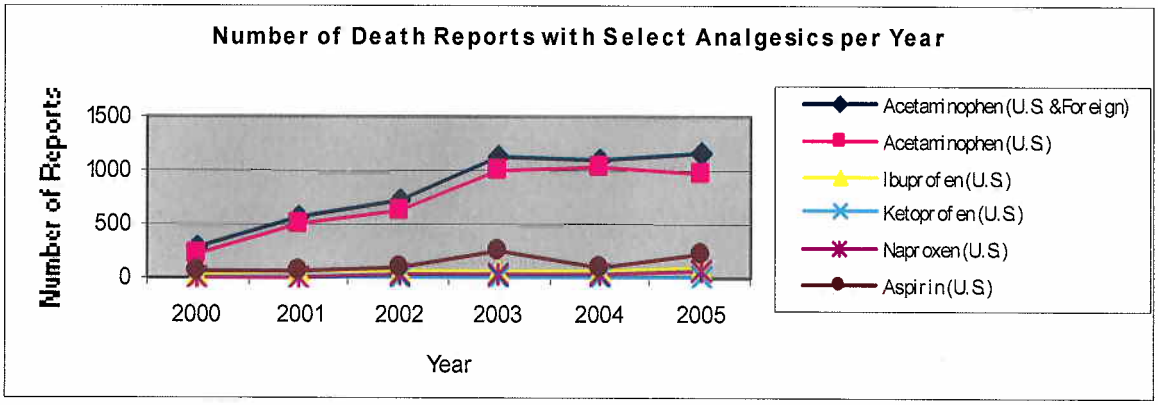
Figure 2. Crude AERS count of all adverse event reports for select analgesics, stratified by year



Acetaminophen consistently leads the number of all adverse event reports compared to the other analgesics (ibuprofen, ketoprofen, naproxen and aspirin), and has trended upwards from 2000 to 2005. The sharp increase in all adverse event reports for aspirin beginning in 2001 and peaking in 2003 is noted, however, the reason for its sudden rise is unclear.

Figure 3 below compares the number of deaths for all adverse events in AERS associated with acetaminophen to several other analgesics, stratified by year.[3]

Figure 3. Crude AERS count of deaths from all adverse events for select analgesics, stratified by year



4 Drug names: suspect only; generic names- acetaminophen, ibuprofen, ketoprofen, naproxen, and aspirin

Acetaminophen has the highest number of deaths compared to the other analgesics (ibuprofen, ketoprofen, naproxen and aspirin) from 2000 to 2005, and is rising at the fastest rate. Acetaminophen also has the highest proportion of deaths to all adverse events, compared to the other selected analgesics.

Listed below are the top 20 most frequently reported adverse events associated with acetaminophen, with death as an outcome, in the U.S. (a report may contain more than one adverse event term):

Table 1. Top 20 adverse event terms (Preferred Terms) for U.S. acetaminophen reports, with death as an outcome (n=5,581)

Preferred Term (PT)	PT Counts	Preferred Term (PT)	PT Counts
Completed suicide	1,961	Accidental overdose	412
Overdose	916	Aspartate aminotransferase increased	369
Multiple drug overdose	784	Alanine aminotransferase increased	331
Intentional overdose	736	Multiple drug overdose intentional	329
Coma	673	Drug level above therapeutic	308
Hepatic failure	549	Intentional drug misuse	301
Cardiac arrest	506	INR increased	282
Drug toxicity	490	Renal failure	264
Hypotension	463	Respiratory arrest	263
Cardio-respiratory arrest	418	Toxicologic test abnormal	256

Completed suicide, overdose, coma and hepatic failure were among the most frequently reported adverse events for acetaminophen with death as an outcome, in the AERS database. Gender was provided in 3,664 of the 5,581 death reports: 1,999 (36%) females, 1,665 (30%) males, and 1,917 (34%) unknown. The age groups were as follows:

Table 2. Reported age groups in U.S. acetaminophen reports, with death as an outcome (n=5,581)

Age Groups	Counts for Death	Age Groups	Counts for Death
0 - <2yrs	93	41 yrs – 50 yrs	1,322
2 yrs – 5 yrs	40	51 yrs – 60 yrs	693
6 yrs – 11yrs	42	61 yrs – 70 yrs	367
12 yrs – 16 yrs	102	71 yrs – 80 yrs	235
17 yrs – 20 yrs	210	81 yrs – 90 yrs	117
21 yrs – 30 yrs	777	91+	14
31 yrs – 40 yrs	1,251	Null age values	318

The highest numbers of death reports are in adults between 30 and 50 years. Only 6% (318 of 5,581) of the reports did not specify the age of the patient.

5.1.2 Liver Toxicity Associated with Acetaminophen

The AERS database was searched for the top 10 drugs associated with hepatotoxicity, by year, using the OSE MedDRA reaction term groupings 1) All Liver Events and 2) Liver Failure.[5] The results are shown in Tables 3 & 4 (The complete list including the numbers of reports can be found in Appendix 1 & 2.)

Table 3. Top 10 drugs associated with OSE MedDRA grouping of "All Liver Events", stratified by year.

MedDRA grouping: All Liver Events					
Cumulative	**2002**	**2003**	**2004**	**2005**	**2006**
APAP	Cerivastatin	Cerivastatin	**APAP**	Rofecoxib	Rofecoxib
Lamivudine	Lamivudine	Bosentan	Bosentan	**APAP**	**APAP**
Troglitazone	Stavudine	**APAP**	Atorvastatin	Atorvastatin	Lamivudine
Rofecoxib	**APAP**	Lamivudine	Rofecoxib	Atomoxetine	Telithromycin
Cerivastatin	Atorvastatin	Infliximab	Infliximab	Lamivudine	Duloxetine
Atorvastatin	Zidovudine	Atorvastatin	Lamivudine	Ribavirin	Atorvastatin
Stavudine	Didanosine	Zidovudine	Leflunomide	Interferon beta 1a	Isotretinoin
Zidovudine	Infliximab	Stavudine	Ezetimibe	Ritonavir	Ritonavir
Simvastatin	Troglitazone	Ezetimibe	Methotrexate	Olanzapine	Simvastatin
Ritonavir	Simvastatin	Simvastatin	Ritonavir	Simvastatin	Ribavirin

As noted in the table above, acetaminophen is the number one drug associated with the cumulative AERS hepatotoxicity reports. In 2002 it was the 4th leading drug to be associated with hepatotoxicity, and since then has trended up the past few years to become the number one drug associated with hepatotoxicity in 2004. Since rofecoxib has been removed from the market, acetaminophen continues to be the number one marketed drug associated with hepatotoxicity.

---

5 AERS reaction terms for OSE MedDRA grouping:
1) All Liver Events:
hepatic and hepatobiliary disorders (HLGT)
hepatobiliary investigations (HLGT)
liver transplant (PT)
2) Liver Failure:
hepatic failure and associated disorders (HLT)
hepatic fibrosis and cirrhosis (HLT)
hepatic necrosis (PT)
hepatitis fulminant (PT)
liver transplant (PT)

Table 4. Top 10 drugs associated with OSE MedDRA grouping of "Liver Failure", stratified by year.

MedDRA grouping: Liver Failure					
Cumulative	**2002**	**2003**	**2004**	**2005**	**2006**
APAP	**APAP**	**APAP**	**APAP**	**APAP**	Rofecoxib
Troglitazone	Troglitazone	Lamivudine	Lamivudine	Ribavirin	**APAP**
Lamivudine	Lamivudine	Rosiglitazone	Rosiglitazone	Atorvastatin	Lamivudine
Stavudine	Stavudine	Ribavirin	Rofecoxib	Lamivudine	Telithromycin
Nevirapine	Nevirapine	Stavudine	Gabapentin	Ritonavir	Duloxetine
Didanosine	Didanosine	Pioglitazone	Ribavirin	Peginterferon alfa 2a	Atorvastatin
Ribavirin	Atorvastatin	Infliximab	Infliximab	Infliximab	Isotretinoin
Atorvastatin	Cerivastatin	Ritonavir	Atorvastatin	Peginterferon alfa 2b	Ritonavir
Methotrexate	Efavirenz	Didanosine	Interferon beta 1a	Rofecoxib	Simvastatin
Ritonavir	Ribavirin	Oxycodone	Methotrexate	Cyclophosphamide	Ribavirin

As shown in the table above, acetaminophen is the number one drug associated with the cumulative AERS liver failure reports and continues to be the leader from 2002 to 2005. Since rofecoxib has been removed from the market, acetaminophen remains the number one marketed drug associated with liver failure for 2006.

Table 5. Crude AERS counts of select adverse events for all NSAIDs since approval[6]

Drug Name / Approval Date	Total AERS Reports	Total AERS Deaths	All Liver Events[3]	Liver Failure[3]
Rx ONLY				
Indomethacin/6-10-1965	5451	742	297	32
Mefenamic acid/3-28-1967	820	102	117	23
Fenoprofen/3-16-1976	2590	93	117	14
Tolmetin/3-24-1976	2114	111	91	15
Sulindac/9-27-1978	4407	307	536	43
Meclofenamate/6-25-1980	583	18	20	2
Piroxicam/4-6-1982	6793	491	411	50
Ketoprofen/1-9-1986	3579	160	190	41
Diclofenac/7-28-1988	11449	1564	1568	213
Etodolac/1-31-1991	3136	105	223	26
Ketorolac/12-20-1991	5048	376	146	28
Nabumetone/12-24-1991	3720	112	177	25
Oxaprozin/10-29-1992	2140	48	107	10
Celecoxib/12-31-1998	22928	1620	831	123
Meloxicam/4-13-2000	1494	169	80	12
Valdecoxib/11-16-2001	7599	559	192	28
Rx and OTC				
Acetaminophen/1960	**25726**	**6809**	**4482**	**1736**
Aspirin/3-28-1972	16688	2017	778	145
Ibuprofen/9-19-1974	23292	1110	891	148
Naproxen/3-11-1976	23603	728	637	112

Table 5 above lists crude counts of total AERS adverse events reports, deaths, and reports related to liver toxicity (all liver events and liver failure) for all NSAIDs since approval. Acetaminophen has the highest number of reports in all categories, but is significantly higher in the liver failure category when compared to the other NSAIDs. There were 1,736 reports of acetaminophen and liver failure; the range for all other NSAIDS was from 2 to 213 reports.

---

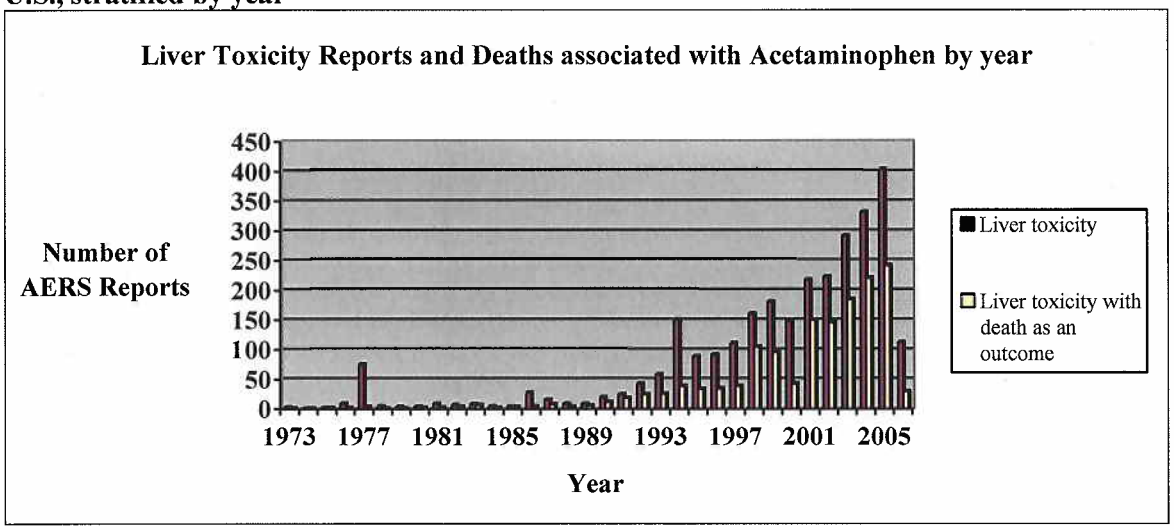
6 AERS search date: October 25, 2006; Search criteria: by active ingredient;
Caveats:

1. Ibuprofen, naproxen, acetaminophen & aspirin: 1) Counts may include adverse event reports for prescription (Rx) and OTC drug products containing ibuprofen, naproxen, acetaminophen, or aspirin; 2) Counts may include reports for combination drug products containing other active ingredients in addition to ibuprofen, naproxen, acetaminophen, or aspirin
2. All drugs listed: 1) Counts may include duplicates; 2) Detailed case review has not been performed so event may or may not be related to NSAIDs.

As of August 17, 2006, a total of 4,317 reports of liver toxicity were identified in the AERS database, of which 2,862 were domestic reports.[7] Of the 2,862 reports, 52% (1,501) had a death outcome. It is important to note that these reports cited the use of single ingredient and/or combination acetaminophen products. These numbers are crude report counts and may include duplicates. Given the large number of reports, individual reviews were not performed to determine an association between the reported event and the use of acetaminophen; these reports may contain concomitant use of other medications.

Figure 4 below depicts the number of domestic liver toxicity reports and deaths in AERS associated with acetaminophen, stratified by year.

Figure 4. Crude AERS count of liver toxicity reports and deaths for acetaminophen in the U.S., stratified by year



The number of domestic acetaminophen liver toxicity reports has trended upwards since the 1990's. The number of liver toxicity reports more than quadrupled in the past decade from 89 in 1995 to 404 in 2005. The number of liver toxicity reports with death as an outcome increased more than 7 fold over the same time period from 34 in 1995 to 242 in 2005. The number of acute liver failure reports and deaths continued to increase from 2004 to 2005 despite the educational effort launched by the Agency in January 2004. The number of acute liver failure reports increased from 332 to 404 in 2004 to 2005, and

7 AERS reaction terms for liver toxicity:
Hepatic and hepatobiliary disorders (HLGT)
Hepatobiliary investigations (HLGT)
Liver transplant (PT)
Hepatic encephalopathy (PT)
Hepatic necrosis (PT)

the number of acute liver failure reports with death as an outcome increased from 221 to 242 in the same time period.

The top 10 most frequently reported liver toxicity PTs associated with acetaminophen, and those with death as an outcome, in the U.S., were hepatic failure, increased AST and ALT, and coma. Gender was provided in 2,756 of the 2,862 reports for liver toxicity: 1,678 (58%) females, 1,078 (38%) males, and 106 (4%) unknown. The highest numbers of reports are in adults between 30 and 50 years (1,159 of 2,862). Nine percent (249 of 2,862) did not specify the age of the patient.

5.1.3 Overdose and Suicide with Acetaminophen

As of August 17, 2006, a total of 6,169 reports of overdose and 2,755 reports of suicidal and self-injurious behavior were identified in the AERS database, of which 5,148 and 2,407 were domestic reports, respectively.[8] Of the 5,148 domestic reports related to overdose, 61% (3,164) had a death outcome; and of the 2,407 domestic reports related to suicidal and self-injurious behavior, 86% (2,080) had a death outcome.

Figures 5 & 6 below depict the number of overdose and suicide reports in AERS associated with acetaminophen, stratified by year. These figures show that adverse event reports (with and without death as an outcome) associated with overdose and suicide have increased significantly since 2000, and have continued to increase from 2004 to 2005 despite the Agency's educational effort in January 2004 to promote the safe use of acetaminophen.

---

8 AERS reaction terms for:
1) Overdose:
prescribed overdose (PT)
overdoses (HLT)
intentional misuse (PT)
2) Suicidal and self-injurious behavior (HLGT) consists of the following PTs:
completed suicide, intentional self-injury, suicidal ideation, suicidal attempt, self-injurious ideation, self-injurious behavior, & self mutilation (& suicidal behavior in 2006)

Figure 5. Crude AERS count of Overdose reports and deaths for acetaminophen in the U.S., stratified by year

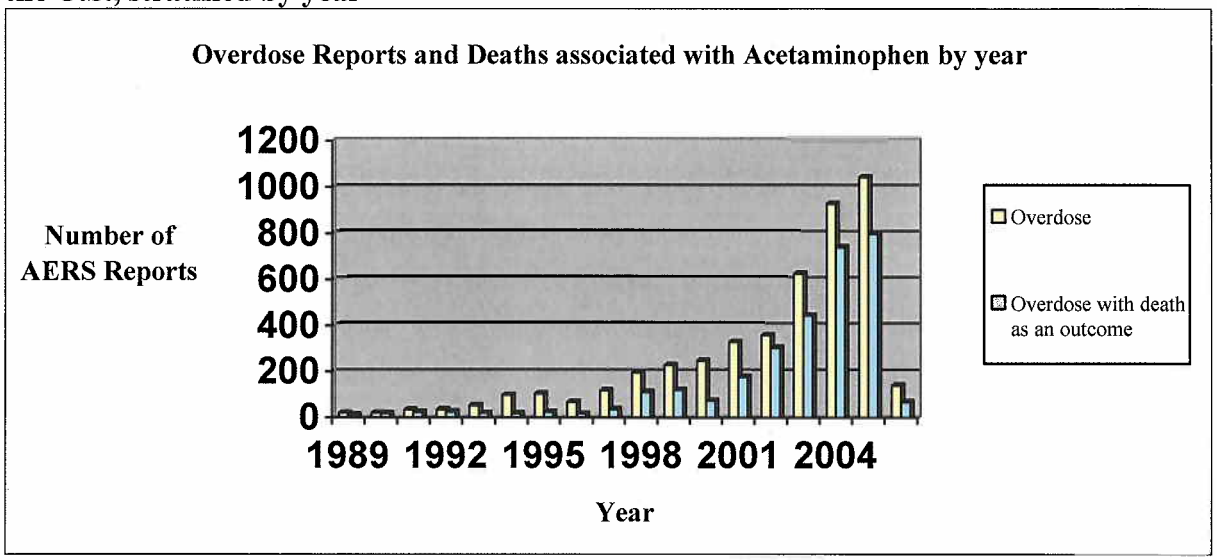


Figure 6. Crude AERS count of Suicidal and Self-injurious Behavior reports and deaths for acetaminophen in the U.S., stratified by year

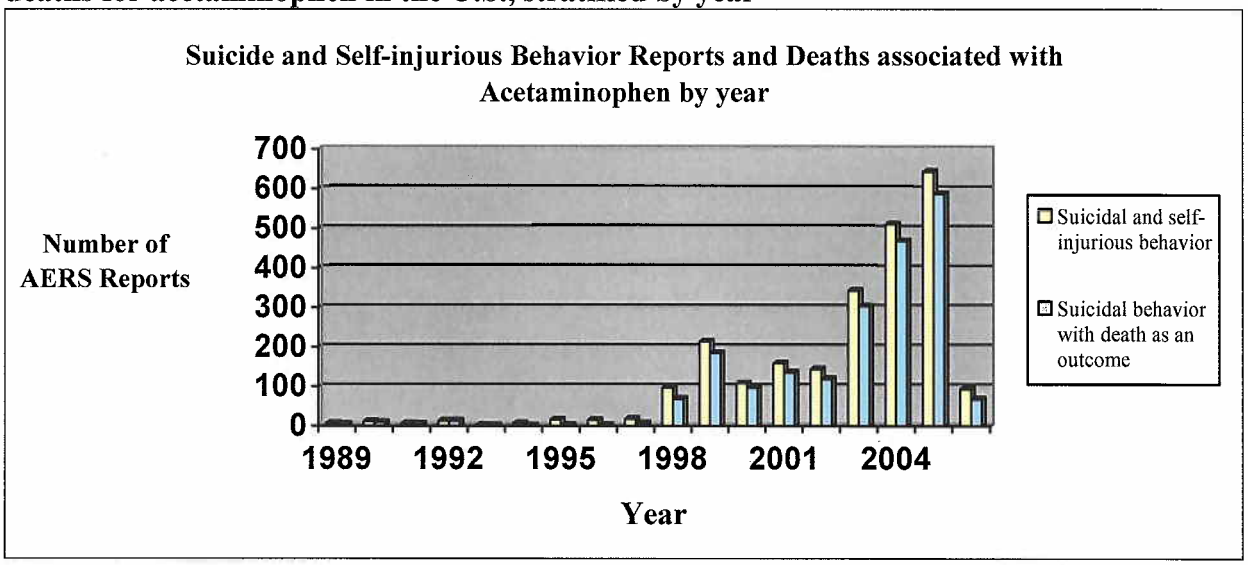
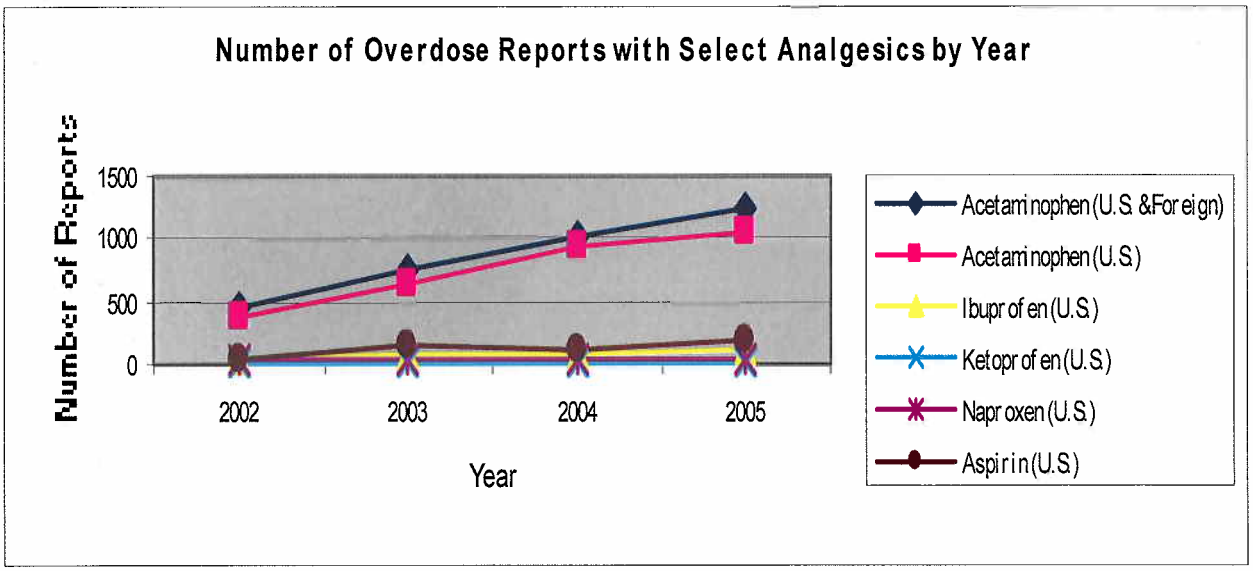


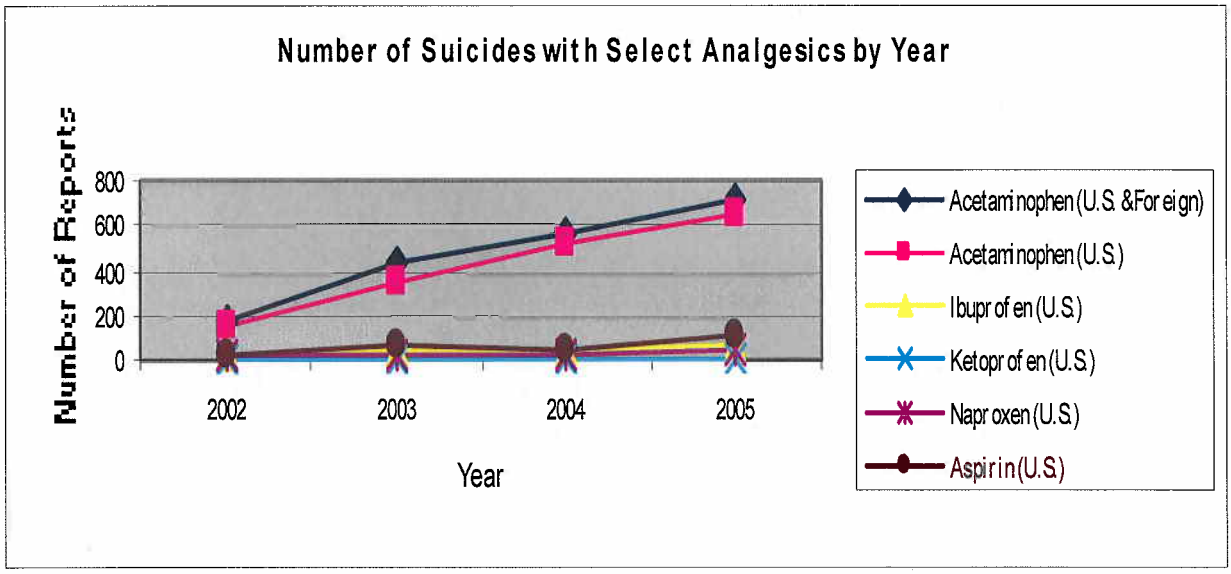
Figure 7 below depicts the number of overdoses in AERS associated with select analgesics, stratified by year.

Figure 7. Crude AERS count of overdoses for select analgesics, stratified by year



As noted in the figure above, acetaminophen has the highest number of overdose reports compared to the other analgesics (ibuprofen, ketoprofen, naproxen and aspirin) from 2002 to 2005, and continues to increase at the fastest rate.

Figure 8. Crude AERS count of suicides for select analgesics, stratified by year



As noted in the figure above, a similar trend is seen with suicide reports as previously noted with overdose reports, where acetaminophen has the highest number of suicide

reports compared to other selected analgesics (ibuprofen, ketoprofen, naproxen and aspirin) from 2002 to 2005 and continues to increase at the fastest rate.

The most frequently reported PTs for overdose reports were overdose (1,669), intentional overdose (1,422), completed suicide (1,358), and multiple drug overdose (1,021). The most frequently reported PTs for suicide related reports were completed suicide (1,963), intentional overdose (559), and multiple drug overdose (442).

Gender was provided in 3,792 of the 5,148 reports for overdose: 2,174 (42%) females, 1,618 (32%) males, and 1,356 (26%) unknown; and in 1,179 of the 2,407 reports for suicidal and self-injurious behavior: 726 (30%) females, 453 (19%) males, and 1,228 (51%) unknown. The highest numbers of reports were found in the age groups between 30 to 50 years.

5.2 SUMMARY OF AERS REVIEW OF 100 DEATH CASES

AERS was searched for acetaminophen and acetaminophen containing products, limited to domestic **death** reports that were submitted to the agency between January 1, 2005 and December 31, 2005. The search yielded a crude count of 1123 cases. Of the 1123 cases, 100 random cases were selected for analysis. Of the 100 random cases, 4 were identified as duplicates for a total of 96 cases.

Criteria for inclusion of cases (72)

- An adverse event of death possibly related to the use of an acetaminophen containing drug product.

Criteria for exclusion of cases (24)

- Reports not found to contain acetaminophen (3)
- Death likely related to co-morbid condition (4)
- Death likely related to co-suspect drug or substance (14)
- Lack of data where the acetaminophen containing product is not the primary suspect (3)

Summary of Cases

Seventy-two (72) cases of death were possibly associated with the use of an acetaminophen containing product.

Table 5.2.1 Selected demographic, outcome, and miscellaneous data based on a sample of all deaths associated with the use of an acetaminophen containing product in AERS cases reported in 2005 (n=72)

Age (n=69)	Mean 42 years, Median 41 years, Range 8 to 83 years
Gender	Male 15, Female 19, Not reported 38
Cause of death	Hepatic failure or necrosis 18 (25%) Cardiac or respiratory event 19 (26%) Not reported 35 (49%)
Hepatic involvement	Hepatic injury* 23 (32%) - (hepatic failure** 21/23)
High APAP levels in the report without mention of liver AEs***	15 (21%)
Reported indication	pain & insomnia 1, back pain 1, ill defined disorder 1, suicide 11, intentional misuse 1, unknown 9, not reported 48
Intent of APAP ingestion (per case narrative)	Suicide 48 (67%) Intentional misuse 11 (15%) Unintentional overdose 4 (6%) Unknown intent 9 (13%)
Category of APAP products (number of total mentions = 81)	Rx Combination Product w/Narcotic (Rx combo w/narc) – 48 (59%) OTC Single Ingredient APAP (SI APAP) - 27 (33%) OTC Combination Product (OTC combo) - 5 (6%) Rx Combination Product w/o narcotic (Rx combo w/o narc) – 1 (1%) {e.g. butalbital/caffeine/APAP}
# APAP products	One - 65 (90%) Two - 6 (8%) Three – 0 Four - 1 (1%)
Dose (n=4)	Entire bottle (unspecified SI APAP) ½ bottle of extended release APAP 4 Tylenol (unspecified SI APAP) 100 propoxyphene/APAP (dose not specified)
Reporter	HCP 52, Consumer 3, Unknown 17

*Cases with hepatic injury had at least 3x ULN ALT or AST, or a diagnosis of liver failure or necrosis without supporting clinical or laboratory data

**Cases with hepatic failure had at least 3x ULN ALT or AST, and PT (INR) >1.5x ULN or elevation of bilirubin >3x ULN. This also includes reports with a diagnosis of liver failure or necrosis without supporting clinical or laboratory data.

***Cases lacked a diagnosis of liver failure and supporting laboratory data, but reported APAP levels within the probable hepatotoxicity profile according to the Rumack-Matthew nomogram or levels >70 mcg/ml.

Over half (53%) of the cases did not report a gender, but of those that did, females accounted for slightly more than males. The patients' age ranged from 8 to 83 years old, with a median of 41 years. There were two patients less than 18 years old, the first was 8 years and the second was 15 years. The case involving the 8 year old was a possible unintentional overdose where the patient received an acetaminophen dose of "pretty regular times 6 days" and had hepatic injury (AST 931 IU/L, ALT 343 IU/L, alkaline phosphatase 411 IU/L, and ammonia 190 IU/L), with unknown cause of death. This case was complicated by concomitant carbamazepine therapy for seizure control with a supratherapeutic level of 30 mcg/ml (therapeutic 4 to 12 mcg/ml). The acetaminophen level was 10 mcg/ml and despite IV n-acetylcysteine administration, she expired on day 13 of her hospitalization. The second pediatric case involved a 15 year old male who ingested an unknown amount of acetaminophen with hydrocodone (intent unknown) and subsequently died. The cause of death was not reported, but was likely due to the narcotic portion of the acetaminophen/hydrocodone product, as evidenced by a high post mortem concentration of hydrocodone of 260 ng/ml (therapeutic 10 to 20 ng/ml) [acetaminophen 41.2 mcg/ml].

Approximately half of the cases (49%, 35/72) did not report a cause of death, and the remaining cases reported hepatic failure or necrosis (25%, 18/72) and cardiac or respiratory event (26%, 19/72) fairly evenly. Three cases that reported cardiac or respiratory event as the cause of death were also found to have hepatic failure. Approximately one-quarter (26%, 19/72) of the deaths were likely due to the narcotic component of the prescription APAP/narcotic combination product. These cases lacked hepatic involvement and had either a high level of hydrocodone ($\geq$70 ng/ml) or reported cardio-respiratory arrest as the cause of death. Of these 19 deaths, 58% (11/19) were intentional overdoses (suicides) while 26% (5/19) were unintentional fatalities. Approximately 32% (23/72) of the cases reported some type of hepatic injury and the majority (21/23) of those cases had hepatic failure or necrosis; only two cases that reported hepatic injury did not qualify as having hepatic failure or necrosis. AST and ALT levels were reported in 22 cases, alkaline phosphatase was reported in 3 cases, and ammonia levels were reported in 8 cases. The mean AST and ALT were 12,157 IU/L (range 14 – 96,501) and 9,538 IU/L (range 20 – 93,301), respectively. The mean alkaline phosphatase level was 261 IU/L (range 176 to 411 IU/L). The mean ammonia level was 137 µmol/L (range 57 – 238). Bilirubin was reported in 9 cases and ranged from 0.5 to 24.2 mg/dl with a mean of 6.27 mg/dl. Baseline liver function tests were not reported in any of the cases. The typical pattern of liver injury in these cases was hepatocellular (3/23); no other patterns (cholestatic or mixed) were identified because of a lack of additional lab data. Viral serology findings were not reported in any of the reports. Autopsy findings of liver injury were reported in 3 cases and the narrative descriptions in each of the cases were as follows: (1) "acute diffuse hepatic necrosis", (2) "fulminant hepatic failure secondary to acute acetaminophen intoxication", and (3) "hepatic steatosis and centrilobular necrosis". Of the 23 cases with hepatic injury, 15 likely had encephalopathy and 18 reported coagulopathy (PT (INR) >1.5xULN). Also among these 23 cases, 1 case reported hepatorenal syndrome, 2 reported renal failure, 1 reported renal

insufficiency, 1 reported azotemia, and 5 reported serum creatinine >3 mg/dl, and 4 reported serum creatinine 2 to 3 mg/dl.

Cases lacking hepatic data or a diagnosis of hepatic failure were analyzed for probable association with acetaminophen toxicity, and approximately 21% (15/72) of the cases were found to have acetaminophen levels within the probable hepatotoxicity profile according to the Rumack-Matthew nomogram or acetaminophen levels >70 mcg/ml with no time frame. An acetaminophen level of 70 mcg/ml was arbitrarily used as a cut-off for likely acetaminophen toxicity based on the Rumack-Matthew nomogram where a value of 70 mcg/ml ten hours post ingestion is the start of probable risk for toxicity. Overall, half (53%, 38/72) of the cases were likely or probably associated with acetaminophen toxicity based on hepatic involvement or high acetaminophen levels, as mentioned above.

Most cases did not report an indication for acetaminophen use. Two cases reported pain (pain & insomnia, and back pain) as an indication, and both cases were unintentional overdoses. The remaining indications were suicide, intentional misuse, and ill defined disorder.

According to the case narratives, suicide and intentional misuse accounted for an overwhelming 82% (59/72) of the cases. The most commonly reported intent for acetaminophen ingestion was suicide (67%, 48/72), followed by intentional misuse (15%, 11/72), unknown intent (13%, 9/72), and unintentional overdoses (6%, 4/72). Unintentional overdose represented the lowest number among the intent of acetaminophen ingestion.

Acetaminophen products were grouped into four general categories as listed in table 5.2.1 (It is further broken down in Table 5.2.2 into more specific product data and intent, to be discussed later in this section). A case may have reported the use of more than one acetaminophen product. A total of 81 acetaminophen containing products were mentioned in the 72 reports. The most reported category was the prescription acetaminophen combination with narcotic, which represented 59% (48/81) of the products mentioned. The next most frequently reported category was OTC single ingredient acetaminophen, which represented 33% (27/81) of the products mentioned. The third most frequent category was the OTC combination product, which accounted for 6% (5/81) of the products mentioned. And finally, the least reported category was the prescription acetaminophen combination without narcotic, which accounted for 1% of the products, and represented only one product (butalbital/caffeine/APAP).

The majority of cases (90%, 65/72) reported use of only one acetaminophen containing product. Approximately 8% (6/72) of the cases reported concomitant use of two acetaminophen containing products and only one case reported concomitant use of four acetaminophen containing products. No case reported concomitant use of more than 4 acetaminophen containing products.

Most cases did not report a dose, except for 4 cases: an entire bottle of unspecified single-ingredient acetaminophen (SI APAP), ½ bottle of extended release acetaminophen, 4 Tylenol® (unspecified SI APAP), and 100 propoxyphene/APAP (dose not specified). Table 5.2.2 breaks down acetaminophen product data into intent: suicide, intentional misuse, unintentional overdose, and unknown intent.

Table 5.2.2 Product information pertinent to acetaminophen containing drug related deaths based on a sample of AERS cases reported in 2005 (n=81, total number of acetaminophen containing products mentioned in the 72 reports)

Category of APAP products by intent				
Category of APAP products (number of total mentions = 81)	Suicide	Intentional misuse	Unintentional overdose	Unknown intent
Rx Combination Product w/Narcotic (Rx combo w/narc) (n=48)	31	9	1	7
OTC Single Ingredient APAP (SI APAP) (n=27)	19	4	2	2
OTC Combination Product (OTC combo) (n=5)	3	1	1	0
Rx Combination Product w/o narcotic (Rx combo w/o narc) (n=1)	1	0	0	0
Break down of the categories by product				
Rx Combination Product w/Narcotic (Rx combo w/narc) (n=48)	Suicide	Intentional misuse	Unintentional overdose	Unknown intent
hydrocodone/APAP	13	7	1	7
codeine/APAP	7	1	0	0
propoxyphene/APAP	6	1	0	0
oxycodone/APAP	5	0	0	0
OTC Single Ingredient APAP (SI APAP) (n=27)	Suicide	Intentional misuse	Unintentional overdose	Unknown intent
not specified	17	4	2	2
"500mg acetaminophen"	1	0	0	0
"extended release acetaminophen"	1	0	0	0
OTC Combination Product (OTC combo) (n=5)	Suicide	Intentional misuse	Unintentional overdose	Unknown intent
diphenhydramine/APAP	1	0	1	0
doxylamine/pseudoephedrine/DM/ APAP	1	0	0	0
aspirin/caffeine/APAP	1	0	0	0
pseudoephedrine/DM/APAP	0	1	0	0
Rx Combination Product w/o narcotic (Rx combo w/o narc) (n=1)	Suicide	Intentional misuse	Unintentional overdose	Unknown intent

butalbital/caffeine/APAP	1	0	0	0

Prescription combination with narcotic represented the most implicated category of acetaminophen products among suicide, intentional misuse, and unknown intent. Approximately 65% (31/48) of the prescription acetaminophen combination with narcotic products involved intentional overdoses (suicide) while 21% (11/48) involved unintentional fatalities. Unintentional fatalities include intentional misuse and unintentional overdose. Single ingredient acetaminophen was the second most implicated category of acetaminophen products among the same group of intent. For unintentional overdose, single ingredient acetaminophen was the most implicated category of acetaminophen products. Among the OTC single ingredient acetaminophen products that were mentioned (n=27), approximately 70% (19/27) involved intentional overdoses (suicide) while 22% (6/27) involved unintentional fatalities. Among the OTC acetaminophen combination products that were mentioned (n=5), approximately (60%) involved intentional overdoses (suicide) while 40% (2/5) involved unintentional fatalities.

The hydrocodone/APAP combination product was the most frequently implicated prescription combination with narcotic overall. The most frequently implicated single ingredient acetaminophen product was the "not specified" category, followed by one report of "500mg" and one report of "extended release". The most frequently implicated OTC combination product was diphenhydramine/APAP. Only one prescription combination without narcotic was implicated, butalbital/caffeine/APAP.

Table 5.2.3 breaks down acetaminophen product data for cases with use of 2 or more acetaminophen products, into intent: suicide, intentional misuse, unintentional overdose, and unknown intent.

Table 5.2.3 Product information in cases of drug related deaths of individuals who used more than one APAP containing formulation, based on a sample of AERS cases reported in 2005 (n=72)

Number of APAP products per case (n=72)	Suicide (n=48)	Intentional misuse (n=11)	Unintentional overdose (n=4)	Unknown intent (n=9)
One (n=65)	44	8	4	9
Two (n=6)	3	3	0	0
Three (n=0)	0	0	0	0
Four (n=1)	1	0	0	0
Cases with 2 or more APAP products (n=7)	**Suicide**	**Intentional misuse**		
Rx combo w/narc + SI APAP	0	2		
Rx combo w/narc + OTC combo	1	0		
Rx combo w/narc + Rx combo w/o narc	1	0		
Two Rx combo w/narc	1	0		

OTC combo + SI APAP	0	1	
Rx combo w/narc + SI APAP + two OTC combo	1	0	

Intentional misuse has the highest percent of cases (27%, 3/11) reporting use of two acetaminophen containing products, compared to the other groups (ranges from 0 to 6%). Approximately 92% (44/48) of suicide cases reported using only one acetaminophen containing product. All 4 of the unintentional overdose cases and 9 unknown intent cases involved the use of only one acetaminophen containing product. One case reported the concomitant use of four acetaminophen containing combination products, and it was in the suicide group. No cases reported the concomitant use of more than four acetaminophen containing products.

Table 5.2.4 Other contributing factors to liver injury in individuals with acetaminophen associated deaths based on a sample of AERS cases reported in 2005

Contributing Factors (n=72)	Suicide	Intentional misuse	Unintentional overdose	Unknown intent
Ethanol Use (Yes - 6, No - 1, Not reported - 65)	5	1*	0	0
Potentially hepatotoxic co-suspect medications (Yes - 3, No - 69)				
Atorvastatin	1	0	0	0
Isoniazid	0	1	0	0
Carbamazepine	0	0	1	0
Exposure to hepatotoxic substance (carburetor & brake cleaner)	1	0	0	0
H/O or underlying liver disease	0	0	0	0

*All of the cases in this table had hepatic involvement, with the exception of this one case of intentional misuse and concomitant ethanol

Table 5.2.4 above lists factors which may have contributed to hepatotoxicity. None of the cases reported a history of liver disease or underlying liver disease. However, six cases (8%) reported the concomitant use of ethanol. Four of 6 patients had a history of alcoholism (2) or chronic alcohol use (2). One case, not included in the table above, did not mention alcohol ingestion but reported a low post mortem blood alcohol level of 0.01gm/100ml (0.08gm/100ml is the national standard blood alcohol limit for drunk driving). Five of the 6 cases reporting ethanol use were in the suicide category, and all reported hepatic injury. The remaining case was an intentional misuse, and reported an unknown cause of death with no hepatic injury.

Sixty-four cases listed one or more concomitant medications, illicit drugs and/or hepatic toxins. Three of the concomitant medications are labeled for hepatic injury. These concomitant, co-suspect medications included atorvastatin, isoniazid, and carbamazepine. All 3 of these cases with co-suspect medications, labeled for hepatotoxic events, reported

hepatic injury. The cases involving atorvastatin and isoniazid reported liver failure as the cause of death; whereas, the case involving carbamazepine reported an unknown cause of death. The case involving carbamazepine reported a supratherapeutic carbamazepine level. Despite the potential hepatotoxicity of the co-suspect medications, all of the 3 cases reported an overdose or possible overdose of acetaminophen, and one case (isoniazid) reported a high acetaminophen level (137mcg/ml); therefore, the role of acetaminophen in causing hepatic injury could not be ruled out in the 3 cases. One case reported the use of co-suspect toxins, carburetor and brake fluid with acetaminophen. This case reported hepatic injury (AST 12,059 IU/L, ALT 4,950 IU/L, total bilirubin 7.1 mg/dl, and INR 3.1), however, the cause of death was cardiac related. It is unclear in all of the 4 cases mentioned above, whether the co-suspect medications were contributing factors, solely related, or not causally related to the deaths.

In 8 of the 72 cases, concomitant medications were not used. Seven of those 8 patients died of liver failure, and the eighth case reported an unknown cause of death with no reports of hepatic injury. Six of those cases were suicide and the remaining 2 were of unknown intent.

6. DATA MINING

A data mining analysis of AERS data was performed on acetaminophen: 1) with all events, 2) hepatic events, 3) overdoses, and 4) suicide. The algorithm used for these analyses was the Multi-item Gamma Poisson Shrinker (MGPS), which analyzes the records contained in large post-marketing drug safety databases and then quantifies reported drug-event associations by producing a set of values or scores which indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayesian Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting rate of an event for a particular drug relative to all other drugs and events in the database being analyzed. MGPS also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95 respectively. DuMouchel W et al 2001, Szarfman A et al 2002).

In this analysis, EBGM values indicate the strength of the reporting relationship between a particular drug and event, as reported in AERS. For example, if EBGM=10 for a drug-event combination, then the drug-event was reported 10 times more frequently in the database than statistically expected when considering all other drugs and events in AERS database as a background "expected." A drug-event combination having an EB05 ≥ 2 indicates 95% confidence that this drug-event combination is reported at least at twice the expected rate when considering all other drugs and events in the database. A drug-event combination having an EB05 > 1 indicates 95% confidence that this drug-event combination is reported at least at a higher-than-expected rate considering all other drugs and events in the database.

6.1 DM Analysis of Hepatic Events, Overdoses, and Suicide

Table 6.1.1 lists EBGM values and confidence limits for the top 20 MedDRA preferred terms (PTs) associated with acetaminophen, in the AERS data.[9] Scores are sorted by EBGM value.

Table 6.1.1. Data Mining Scores for all adverse events with acetaminophen, CBAERS Database; (run 449; data current as of September 29, 2006)

Ingredient	PT	EBGM	EB05	EB95	N
Acetaminophen	Endothelin increased	37.0	19.4	65.1	8
Acetaminophen	Analgesic drug level above therapeutic	33.5	28.5	39.2	107
Acetaminophen	Adrenogenital syndrome	32.1	18.2	53.1	10
Acetaminophen	Gastrointestinal ischaemia	23.5	12.7	39.6	10
Acetaminophen	Arrhythmia supraventricular	22.4	20.4	24.4	348
Acetaminophen	Analgesic drug level increased	22.1	16.7	28.8	37
Acetaminophen	Alpha tumour necrosis factor increased	21.0	5.7	43.2	7
Acetaminophen	Fear of disease	16.6	14.0	19.4	103
Acetaminophen	Renal papillary necrosis	14.6	9.6	20.8	23
Acetaminophen	Blood pH decreased	12.7	11.5	14.1	268
Acetaminophen	Anion gap increased	12.2	9.6	15.0	62
Acetaminophen	Hepatorenal failure	11.0	7.8	14.6	39
Acetaminophen	Incorrect drug dosage form administered	10.8	4.8	20.7	12
Acetaminophen	PO2 increased	10.4	8.1	13.0	63
Acetaminophen	Hepatic necrosis	10.0	9.2	10.9	386
Acetaminophen	Blood bicarbonate decreased	9.3	8.1	10.7	153
Acetaminophen	Ammonia increased	9.0	7.7	10.5	134
Acetaminophen	Pupil fixed	9.0	7.7	10.4	138
Acetaminophen	Hepatic failure	8.9	8.5	9.4	1209
Acetaminophen	Toxicologic test abnormal	8.6	7.7	9.5	252

N = number of cases
Highlighted cases include hepatic events and events which could impact hepatic events.

As noted in the table above, high association scores (EBGM >8) are seen with PT's involving hepatic events, including hepatorenal failure (EBGM=11.0), hepatic necrosis (EBGM=10.0), and hepatic failure (EBGM=8.9). Hepatic failure represents the largest number of cases (N=1209). High association scores are also seen with PT's which could impact hepatic events, such as analgesic drug level above therapeutic (EBGM=33.5), analgesic drug level increased (EBGM=22.1), and toxicologic test abnormal (EGBM=8.6).

9 Search terms:
Ingredient: acetaminophen
MedDRA term: all HLT (then selected out those HLTs related to hepatic, overdoses, and suicide)

7. EPIDEMIOLOGICAL CONSIDERATIONS

To help evaluate the effectiveness of the acetaminophen-related educational effort, OSE reviewed the literature on the subject of acetaminophen risk management strategies, and updated earlier analyses of acetaminophen-related overdoses from two national databases.

7.1 Literature review

Toxic effects from acetaminophen have been reported extensively in the literature. One of the most recent studies provided an epidemiologic summary from a national acute liver failure (ALF) surveillance program and was published in late 2005 by Larson et al. The study covered the period January 1998 to December 2003 and collected clinical and demographic information from 22 academic centers. There were 662 patients with ALF from any cause enrolled in the study with strikingly 275 (42%) reported to have acetaminophen-related hepatotoxicity. About half (147) of the 275 patients used only over-the-counter acetaminophen and about half (120) used a prescription acetaminophen product. Among those patients whose intent was known, 122 (44%) reported an intentional overdose. Other findings included: 1) there was a higher use of narcotic/acetaminophen combination products among the unintentional group (63%) compared to the intentional group (18%), 2) 19 (7%) patients reported taking less than 4 grams of acetaminophen per day prior to their symptoms, 3) 155 (55%) used alcohol chronically, and 4) the percent of patients with acetaminophen-related ALF among patients with ALF from any cause has increased from 28% in 1998 to 51% in 2003

A 2004 review of national databases provided estimates of the number of acetaminophen-related overdoses in the United States (Nourjah P et al 2006). The authors reported estimates from emergency department visits (averaged for the years 1993-1999), hospitalizations (averaged for the years 1990-1999), and mortality data (averaged for the years 1996-1998) of 56,000, 26,000 and 458 annually, respectively. An estimated 8 to 26% of overdoses were thought to be unintentional.

RISK MANAGEMENT EFFORTS OUTSIDE OF THE U.S.

In September 1998, the United Kingdom began a program to limit the amount of acetaminophen available over-the-counter; the product became available in blister-packs. Two types of packs were made available – the Supermarket packs contained 16 tablets (500 mg each) and the pharmacy packs contained 32 tablets. A prescription was needed to purchase more than 100 tablets at a time (Turvill JL et al, 2000). These changes were made because of concerns that many of the overdoses that occurred were impulsive and blister-packs with limited quantity might decrease the high rate of acetaminophen-related suicides in the UK. An earlier study of 80 patients who chose acetaminophen for overdose reported that 33 (41%) had seriously contemplated taking the overdose for less than one hour beforehand and another 26 (33%) for up to 3 hours (Hawton K et al, 1996). Thirty-three (41%) had obtained the tablets less than an hour before taking the overdose.

Forty-three cases (54%) found the tablets in a usual location in the house. The effectiveness of blister-packs as an intervention is difficult to interpret by this study which reported that 60% of his 80 interviewed patients used acetaminophen doses obtained from blister packs (similar to the current sales of blister packs in the U.K. at the time - 55%) and those patients who took more than 25 tablets, were significantly more likely to use loose pills rather than blister-packs (69% versus 40%); but the investigator also reported that 21 (66%) of those who did not use a blister-pack still would have overdosed on acetaminophen if blister packs were all that was available. A second report by Hawton from the same group of patients found that most did not know that the harmful effects were delayed, with only 18 (22%) realizing the effects would take more than 24 hours (Hawton K et al, 1995).

Australian investigators presented their study of the effects of limiting the available tablets of carbamazepine and using strip packaging; this study of a total of 67 patients (51 before and 16 after the 1993 change) showed the number of reported tablets used decreased and the amounts of carbamazepine decreased (although the proportion of patients with coma, the proportion of patients requiring intubation and the time in hospital did not differ significantly) (Buckley NA et, 1995). An analysis by Gunnell et al looked at the worldwide availability of acetaminophen by analyzing questionnaires from 12 poisons centers and 5 psychiatrists and by completing a literature review from 23 countries (Gunnell D et al, 2000). Gunnell concludes that acetaminophen-related mortality is higher in countries without restrictions, although he acknowledges that his conclusions are based on limited data and not completely consistent, for example, he notes that Sweden had limited access to acetaminophen and relatively high mortality rates. Gunnell suggests that mortality from acetaminophen may be related to a number of different factors, not just access.

As a risk minimization intervention, the introduction of blister packs in the UK is one that has been studied and reported by a number of investigators. The analyses of this strategy have resulted in different findings. (Appendix 3) Many of the studies from the UK (and other countries) suggest there might be some benefit from restriction of the number of tablets and blister-packs, with a 21 % reduction in deaths (Hawton K et al, 2001) 30-50% reduction in severe hepatotoxicity (Hawton K et al 2001, Hughes B et al, 2003), 31 % reduction in admissions (Hughes B et al, 2003) and a 11 % reduction in non-fatal overdoses (Hawton K et al, 2001). Other studies did not find a significant reduction in admissions or days of hospital stay (Robinson D et al, 2000, Thomas MR et al, 2001) and one study reported an increase in overdoses (Bateman DN et al, 2006). The concerns of some that overdoses would switch to other drugs was not supported by some (Turvill JL et al, 2000, Kisely SR et al, 2003), but was supported by others (Thomas MR et al, 2001, Balit CR et al 2002). None of the studies provided overdose information by intention, so it is not clear if any of the reported changes occurred among intentional overdoses or all types of overdoses. Overall, it is difficult to make a summary conclusion given the different study limitations, but there is some suggestion that restriction of the number of tablets and blister-packs may be beneficial.

TRENDS IN ACETAMINOPHEN RELATED TOXICITY BEFORE AND AFTER IMPLEMENTATION OF THE EDUCATIONAL PROGRAM

7.2 Toxic Exposure Surveillance System (TESS)

The Toxic Exposure Surveillance System or TESS is a poisoning surveillance database maintained by the American Association of Poison Control Centers (AAPCC) in cooperation with 61 poison control centers in the U.S. In 2005 (the latest year for which we have data), poison control centers linked with AAPCC served nearly 296 million of the U.S. population. Since 1983 when TESS was started, to the present time, this database contains 41 million human poison exposure cases including 2.4 million cases reported in 2005 alone.

7.2.1 Methods

The AAPCC's annual reports of 2003, 2004 and 2005 that summarize TESS data were reviewed to determine the extent of poisoning in association with exposure to acetaminophen prescription combination and over-the-counter products. Only those cases were included that listed acetaminophen as the primary (first) agent. Two tables in the annual reports (Table 21: Summary of Fatal exposures, and Table 22B: Demographic Profile of Exposure Cases by Generic Category of Substances and Products) were reviewed and formed the basis of this report.

Definitions and terminology used:

In the annual reports, '*major effect*' is defined as signs or symptoms occurring as a result of the exposure that were life-threatening or resulted in significant residual disability or disfigurement. '*Death*' is when a patient dies as a result of the exposure or as a direct complication of the exposure. Only those deaths that are probably or undoubtedly related to the exposure are coded in TESS.

The various reasons for exposure are defined here. '*Intentional misuse*' is an exposure resulting from the intentional improper or incorrect use of a substance for reasons other than the pursuit of a psychotropic effect. '*Intentional abuse*' is an exposure resulting from the intentional improper or incorrect use of a substance where the victim was likely attempting to achieve a euphoric or psychotropic effect. All recreational use of substances for any effect is included. '*Intentional unknown*' is an exposure that is determined to be intentional but the specific motive is unknown. '*Unintentional unknown*' is an exposure determined to be unintentional but the exact reason is unknown. '*Unintentional general'* includes all unintentional exposures not specifically defined. '*Adverse reaction*' is defined as an adverse event occurring with normal, prescribed, labeled or recommended use of the product, as opposed to overdose, misuse or abuse. Included are cases with an unwanted effect caused by an allergic, hypersensitive, or idiosyncratic response to the active ingredients, inactive ingredients, or excipients. Concomitant use of a contraindicated medication or food is excluded, and coded instead

as a therapeutic error. '*Therapeutic error*' is defined as an unintentional deviation from a proper therapeutic regimen that results in the wrong dose, incorrect route of administration, administration to the wrong person, or administration of the wrong substance. Only exposures to medications or products substituted for medications are included. Drug interactions resulting from unintentional administration of drugs or foods which are known to interact are also included. *'Suspected suicidal'* is defined as an exposure resulting from the inappropriate use of a substance for reasons that are suspected to be self-destructive or manipulative.

Acute exposure is defined as a single, repeated or continuous exposure occurring over a period of 8 hours or less. *Chronic exposure* is defined as a continuous, repeated or intermittent exposure to the same substance in a period exceeding 8 hours. *Acute-on-chronic* is defined as a single exposure preceded by a continuous, repeated or intermittent exposure occurring over a period exceeding 8 hours.

In summarizing the reasons for acetaminophen intake in cases which resulted in fatalities, we combined the categories of *unintentional unknown*, *therapeutic error*, and *intentional misuse* in a general category as 'Unintentional'. We included *intentional misuse* since these were not classified as suicides, and were assumed likely to represent individuals who ingested excessive acetaminophen with therapeutic intent, such as pain or fever relief.

Health care facilities include acute care hospitals, physician offices or clinics, and freestanding emergency centers. Non-health care facility refers to the site of exposure that is usually the patient's home.

7.2.2 Results

Tables 7.2.1 and 7.2.2 summarize acetaminophen exposures by type of over-the-counter (OTC) formulation, gives a breakdown of unintentional exposure, number of individuals treated in a health care facility, and whether there was a major effect for the three year period 2003-2005. In the study period, about 66% of acetaminophen single ingredient exposure was unintentional or accidental in nature of which about 43% were treated in a health care facility and about 3% experienced major effect. The numbers of exposures have increased over time, but the numbers with a major effect have decreased.

Table 7.2.1 Exposures to Acetaminophen OTC* Single Ingredient Products, TESS

Year	Total	Unintentional (%)	Treated in HCF** (%)	***Major Effect (%)
2003	61,902	40,833 (66)	25,964 (42)	3,372 (5)
Education program January 2004				
2004	62,542	40,424 (65)	27,270 (44)	1,024 (2)
2005	67,531	44,727 (66)	29,885 (44)	1,187 (2)

*OTC=Over-the-counter; **HCF=Healthcare facility

***Major Effect: signs or symptoms occurring as a result of the exposure were life-threatening or resulted in significant residual disability or disfigurement.

With respect to acetaminophen OTC combination products with aspirin and other ingredient, the total number of exposures saw an increase from 6,490 in 2003 to over 7,000 each in 2005. About half of the exposures were unintentional and were treated in a health care facility.

Table 7.2.2 Exposures to OTC Acetaminophen containing Combination Products with Aspirin and other Ingredients, TESS

Year	Total	Unintentional (%)	Treated in HCF (%)	Major Effect (%)
2003	6,490	3,260 (50)	3187 (49)	43 (<1)
Education program January 2004				
2004	6,922	3,558 (51)	3,438 (50)	34 (<1)
2005	7,083	3,660 (52)	3,845 (54)	41 (<1)

*OTC=Over-the-counter; **HCF=Healthcare facility

***Major Effect: signs or symptoms occurring as a result of the exposure were life-threatening or resulted in significant residual disability or disfigurement.

Tables 7.2.3 and 7.2.4 show a 3-year (2003 to 2005) comparison of fatal exposure to acetaminophen as single ingredient OTC product, and OTC acetaminophen combination products respectively. Fatal exposures with single ingredient acetaminophen products have declined slightly from 114 in 2003 to 96 in 2005. Nearly half of these were acute exposures. About 60% of these exposures were with suicidal intent and another 25% unintentional or accidental. There has been very little variation (22 deaths in 2003 and 20 in 2005) in the total number of fatal exposures with OTC acetaminophen combination products in the three-year period. Majority of these (70% in 2005) exposures were with suicidal intent and about 5% unintentional or accidental.

Table 7.2.3 Fatalities in Association with OTC Acetaminophen Single Ingredient Products, TESS

Year	Total	Acute Exposure* (%)	Acute/Chronic Exposure (%)	Suicide (%)	Unintentional** (%)
2003	114	53 (46)	14 (12)	71 (62)	26 (23)
Education program January 2004					
2004	110	54 (49)	11 (10)	69 (63)	20 (18)
2005	96	47 (49)	9 (9)	57 (59)	25 (26)

*Acute exposure = single, repeated or continuous exposure occurring over a period of 8 hours; acute/chronic = single exposure preceded by a continuous, repeated or intermittent exposure occurring over a period exceeding 8 hours.

** Unintentional= Unintentional unknown, therapeutic error and intentional misuse

Table 7.2.4 Fatalities in Association with OTC Acetaminophen containing Combination Products, TESS

Year	Total	Acute Exposure* (%)	Acute/Chronic Exposure (%)	Suicide (%)	Unintentional** (%)
2003	22	11 (50)	4 (18)	18 (82)	0
Education program January 2004					
2004	22	16 (72)	2 (9)	20 (91)	1 (4)
2005	20	14 (70)	2 (10)	14 (70)	1 (5)

*Acute exposure = single, repeated or continuous exposure occurring over a period of 8 hours; acute/chronic = single exposure preceded by a continuous, repeated or intermittent exposure occurring over a period exceeding 8 hours.

** Unintentional= Unintentional unknown, therapeutic error and intentional misuse

Table 7.2.5 summarizes exposures of acetaminophen combination products with narcotic for the 3-year period (2003 to 2005). There was very little variation in the total number of exposures in this period (37,088 in 2003 and 41,999 in 2005). In 2005, of the nearly 42,000 exposures, about 1/3rd were unintentional, and about 2/3rd of these cases resulted in treatment in a health care facility. Only three per cent of the cases experienced major effects.

Table 7.2.5 Exposures to Acetaminophen containing Combination Narcotic Products, TESS

Year	Total	Unintentional (%)	Treated in HCF (%)	Major Effect (%)
2003	37,088	13,282 (36)	21,853 (59)	1,147 (3)
Education program January 2004				
2004	41,584	14,622 (35)	24,508 (59)	1,302 (3)
2005	41,999	14,327 (34)	27, 519 (65)	1,470 (3)

*OTC=Over-the-counter; **HCF=Healthcare facility

***Major Effect: signs or symptoms occurring as a result of the exposure were life-threatening or resulted in significant residual disability or disfigurement.

Table 7.2.6 summarizes fatal exposures with prescription acetaminophen combination products in the 3-year period (2003 to 2005). There has been very little variation in the total number of fatalities in the study period with 78 deaths in 2003 and 72 in 2005. Majority of the deaths (about 2/3rd in 2005) followed intake of acetaminophen with suicidal intent and about 10% were unintentional or accidental.

Table 7.2.6 Fatalities in Association with Acetaminophen containing Combination Narcotic Products, TESS

Year	Total	Acute Exposure* (%)	Acute/Chronic Exposure (%)	Suicide (%)	Unintentional** (%)
2003	78	35 (45)	27 (35)	50 (64)	8 (10)
Education program January 2004					
2004	86	38 (44)	32 (37)	64 (74)	11 (13)
2005	72	23 (32)	21 (29)	46 (63)	8 (11)

*Acute exposure = single, repeated or continuous exposure occurring over a period of 8 hours; acute/chronic = single exposure preceded by a continuous, repeated or intermittent exposure occurring over a period exceeding 8 hours.

** Unintentional= Unintentional unknown, therapeutic error and intentional misuse

The analysis of calls to Poison Centers show a continued increase, but stability in the proportion of unintentional calls, the percent treated in a healthcare facility and the percent with a major effect. The numbers of calls that result in a fatality does not seem to change when viewed by product category, but when all acetaminophen products are combined the numbers have decreased from 214 in 2003 to 188 in 2005.

7.3

Outdated material has been redacted and updated information will be presented at the advisory committee meeting.

Outdated material has been redacted and updated information will be presented at the advisory committee meeting.

Outdated material has been redacted and updated information will be presented at the advisory committee meeting.

Outdated material has been redacted and updated information will be presented at the advisory committee meeting.

8. CONCLUSION

AERS DATA - CRUDE COUNTS

- Acetaminophen is currently the number one marketed drug associated with acute liver failure and serious and life-threatening hepatotoxicity in the AERS database.
- According to AERS crude counts, the number of all adverse events, deaths, liver toxicity, overdose, and suicide in association with acetaminophen has trended upwards since the late 1990's to the mid 2000's.
- The crude number of acute liver failure reports submitted to AERS more than quadrupled in the past decade from 89 in 1995 to 404 in 2005. The number of liver toxicity reports with death as an outcome increased more than 7 fold over the same time period from 34 in 1995 to 242 in 2005.
- The crude number of acute liver failure reports and deaths, overdose, and suicide in AERS continued to increase from 2004 to 2005 despite the educational effort launched by the Agency in January 2004.
- Acetaminophen has the highest number of domestic reports of death from all causes compared to ibuprofen, ketoprofen, naproxen, and aspirin, and continues to increase at the highest rate.
- Data mining analysis is consistent with AERS data in that acetaminophen has high association scores (EBGM>8) with various MedDRA PTs related to clinically significant hepatic events (hepatorenal failure, hepatic necrosis, hepatic failure, hepatic encephalopathy, coma hepatic, liver transplant, and hepatotoxicity).

AERS REVIEW OF 100 DEATH CASES FROM 2005

- Approximately half (53%) of the cases were likely or probably associated with acetaminophen toxicity based on hepatic involvement or high acetaminophen levels.
- Suicide and intentional misuse accounted for 82% of the cases.
- Approximately one-quarter (26%) of the deaths were likely due to the narcotic component of a prescription acetaminophen/narcotic combination product. Of these deaths, 58% (11/19) were intentional overdoses (suicides) while 26% (5/19) were unintentional fatalities.
- The most reported category of acetaminophen containing products was the prescription acetaminophen combination with narcotic (59%) followed by the over-the-counter (OTC) single ingredient acetaminophen (33%).
- More than half of the acetaminophen containing products in the prescription acetaminophen combination with narcotic category (65%) and OTC single ingredient acetaminophen category (70%) involved intentional overdoses (suicide) while unintentional fatalities were much lower (prescription acetaminophen combination with narcotic 21% and OTC single ingredient acetaminophen 22%).
- The majority of cases (90%) reported use of only one acetaminophen containing product.

EPIDEMIOLOGIC DATA

- As a risk management intervention, the introduction of blister packs in the UK is one that has been studied and reported by a number of investigators. Analyses of the effectiveness of this strategy have yielded different findings.(Appendix 3). Although many of the studies from the UK suggest there might be some benefit from restriction of the number of tablets and blister-packs, other studies did not find a significant reduction in admissions or days of hospital stay and one study actually reported an increase in overdoses. The concern that people with overdoses would switch to other non-acetaminophen drugs was not supported by some but was supported by others.
- Calls to Poison Control centers have increased for single ingredient, OTC combination, and prescription acetaminophen-containing products.
- The numbers of calls resulting in fatality have not changed drastically when analyzed by product category; nonetheless, when all acetaminophen products are combined the numbers have decreased from 214 in 2003 to 188 in 2005.
- Calls to Poison Control centers show a difference in the proportion of people with intentional versus unintentional overdose between OTC and prescription acetaminophen products; 66% of single ingredient products calls and 52% of OTC combination products calls were unintentional, while 34% of prescription acetaminophen products calls were unintentional.

Outdated material has been redacted and updated information will be presented at the advisory committee meeting.

RECOMMENDATIONS

In addition to the above findings, an extensive review of risk minimization efforts in the U.K. and, to some extent, in other countries suggests that certain strategies may decrease the number of reports of morbidity and mortality associated with acetaminophen misuse. The following recommendations are being proposed for consideration. These have been ranked in the order of ease with which they can be implemented.

1. Expanded Educational Efforts:

In January 2004, FDA launched a consumer educational campaign to promote safe use of acetaminophen which doesn't appear to have had any major impact in reducing the problems associated with acetaminophen as evidenced by the current review. In December 2006, FDA proposed to amend labeling regulations for over-the-counter acetaminophen products which will require new warnings to highlight the potential for hepatotoxicity particularly in association with the usage of high dose acetaminophen, when multiple acetaminophen products are taken concomitantly, and in the setting of moderate alcohol intake. While the proposed rule addresses issues with labeling of OTC products containing acetaminophen, it does not include educational efforts. *These proposed amendments should be accompanied by expanded educational efforts directed to both the consumers and the health care professionals to enhance and promote safe use of acetaminophen products. Examples would be public service announcements in the newspapers, popular magazines, as well as doctor office and pharmacy flyers and posters, and radio and television advertisements.*

2. Reduction of Pack Size/Blister Pack:

A number of countries in Europe (United Kingdom, Germany, France, Sweden, Switzerland, and Belgium) have restricted the total number of acetaminophen tablets that can be sold over-the-counter to prevent acetaminophen misuse. Overall, it is difficult to make a summary conclusion about the overall effectiveness of this approach given the different study limitations, but there is some suggestion that restriction of the number of tablets and blister-packs may be beneficial. Many of the studies from the UK (and other countries) suggest there might be some benefit from restriction of the number of tablets and blister-packs, with a 21 % reduction in deaths, a 30-50% reduction in severe hepatotoxicity, a 31 % reduction in admissions and an 11 % reduction in non-fatal overdoses. On the other hand, some other studies did not find a significant reduction in admissions or days of hospital stay and one study reported an increase in overdoses. *Taken together, given that there is some suggestion that there may be benefit to this intervention, reducing the pack size of acetaminophen products and availability of blister package should be considered.*

3. Reduction in Maximum Recommended Dosage/Maximum Strength:

Evidence suggests that there is a relatively narrow margin between the maximum recommended daily dose of 4 grams of acetaminophen and doses that are associated with hepatotoxicity. Bearing in mind that the minimum toxic dose of acetaminophen has been as low as 6 g per day in some cases (Paul Freie H 2000), consideration should be given to reduce the maximum daily dosage from 4 grams to 3 grams (QID to TID) for acute pain control, and also to reduce the maximum tablet and capsule strength of acetaminophen to 325 mg. According to the Proposed Rule for 21 CFR Parts 201 to 343 in the Federal Register of December 26, 2006, there is AERS data to raise concern that a maximum daily dose of 4 grams may not be safe for at risk subpopulations, but the data is limited on which subpopulations are at risk and what is considered a safe dose. *Therefore, consideration should be given to decrease the currently labeled maximum daily dose of 4 grams because this implies that it is generally recognized as safe and effective for use in the general population.*

In addition, reducing the maximum tablet and capsule strength of acetaminophen to 325mg should be considered in light of the current safety issue with acetaminophen toxicity and liver failure. According to the Proposed Rule for 21 CFR Parts 201 to 343 in the Federal Register of December 26, 2006, the rationale for marketing 500 mg tablets in 1973 was that the higher strength would have greater analgesic efficacy, and two of four double-blind, placebo-controlled post partum pain studies demonstrated that two 500 mg capsules (1000 mg) was significantly more effective than a single dose of two 325 mg tablets (650 mg). Further analysis to determine whether these studies would stand up to the current standard for clinical trials and risk versus benefit analysis of today should be undertaken, bearing in mind the safety issues that have come to light.

4. Unbundle Prescription Combination Products:

Keeping in view that prescription narcotic combination acetaminophen products comprise a significant proportion of patients who develop drug-induced acute liver failure, with Larson et al finding that 53% of their study patients ingested prescription acetaminophen/narcotic compounds and 79% of those with prescription acetaminophen/narcotic overdoses were unintentional, *consideration should be given to unbundling these combination products.* Removing acetaminophen from acetaminophen/opiate combination products is expected to decrease the number of unintentional overdoses and unintended outcomes that result from acetaminophen toxicity. Opiate and acetaminophen combination products are widely prescribed, and the hydrocodone/acetaminophen combination product is the number one dispensed prescription product, which is troubling since the opiate component of the drug has a high addictive and tolerance profile requiring increasing doses of the opiate to maintain pain control, thereby inadvertently increasing acetaminophen and causing a hitchhiker effect. By unbundling these narcotic combination products, prescribers will have to prescribe single ingredient opiate and/or single ingredient acetaminophen products separately with instructions to take them together, if appropriate. The patient may be inconvenienced by

having to take two or more tablets versus one and the prescribing patterns of providers may potentially shift to other drugs causing an increase in unintended adverse events from other products. These potential effects do not change the fact that the benefit of reducing acetaminophen overdose and toxicity in the population overall will have a positive public health impact. Most narcotic and acetaminophen combinations are schedule 3 and unbundling it will result in a single ingredient narcotic which is currently schedule 2; however, this should not be an unreasonable barrier for prescribers and patients in having access to each component of these products.

10. REFERENCES

Balit CR, Isbister GK, Peat J, Dawson AH, Whyte IM. Paracetamol recall: a natural experiment influencing analgesic poisoning. Med J Aust 2002; 176: 162-165.

Bateman DN, Gorman DR, Bain M, Inglis JHC, House FR, Murphy D. Legislation restricting paracetamol sales and patterns of self-harm and death from paracetamol-containing preparations in Scotland. Br J Clin Pharmacol 2006; 62: 573-581.

Buckley NA, Newby DA, Dawson AH, Whyte IM.. The effect of the introduction of safety packaging for carbamazepine on toxicity in overdose in adults. Pharmacoepidemiol Drug Saf 1995; 4: 351-354.

Dargan P, Jones A. Effects of legislation restricting pack sizes of paracetamol on self poisoning. BMJ 2001; 322: 553-2.

DuMouchel W, Pregibon D. Empirical bayesian screening for multi-item associations. Proceedings of the conference on knowledge discovery and data; 2001 Aug 26-29; San Diego (CA): ACM Press: 67-76.

Gunnell D, Murray V, Hawton K. Use of paracetamol for suicide and nonfatal poisoning: worldwide patterns of use and misuse. Suicide Life Threat Behav 2000; 30: 313-326.

Hawton K, Ware C, Mistry H, Hewitt J, Kingsbury S, Robberts D, Weitzel H. Why patient choose paracetamol for self poisoning and their knowledge of its dangers. BMJ 1995; 310: 164.

Hawton K, Ware C, Mistry H, Hewitt J, Kingsbury S, Roberts D, Weitzel H. Paracetamol self-poisoning: Characteristics, prevention and harm reduction. Br J Psychiatry 1996; 168:43-48.

Hawton K, Townsend E, Deeks J, Appleby L, Gunnell D, Bennewith O, Cooper J. Effects of legislation restricting pack sizes of paracetamol and salicylate on self poisoning in the United Kingdom: before and after study. BMJ 2001; 322: 1-7.

Hawton K, Simkin S, Deeks J, Cooper J, Johnston A, Waters K, Arundel M, Bernal W, Gunson B, Hudson M, Suri D, Simpson K. UK legislation on analgesic packs: before and after study of long term effect on poisonings. BMJ 2004; 329: 1076.

Hughes B, Durran A, Langford NJ, Mutimer D. Paracetamol poisoning – impact of pack size restrictions. J Clin Pharm Ther 2003; 28: 307-310.

Kisely SR, Lawrence D, Preston NJ. The effect of recalling paracetamol on hospital admissions for poisoning in Western Australia. Med J Aust 2003; 178: 72-74.

Larson AM, Polson J, Fontana, RJ, Davern TJ, Lalani E, Hynan LS, Reisch JS, Schiødt FV, Ostapowicz, Shakil O, Lee, WM and ALFSG. Acetaminophen-induced acute liver failure: results of a United States Multicenter, prospective study. Hepatology 2005; 42: 1364-1372.

Nourjah P, Ahmad SR, Karwoski C, Willy M. Estimates of acetaminophen (Paracetamol)-associated overdoses in the United States. Pharmacoepidemiol and Drug Saf 2006; 15: 398-405.

Paul Freie HM. Chapter 9.1. Antipyretic analgesics. In: Meyler's Side Effects of Drugs, pp. 240-245, 14th edition, 2000, Elsevier, Amsterdam.

Poulin C. Prevention of paracetamol poisoning. Lancet 2000; 355: 2009-2010.

Prince MI, Thomas SHL, James OFW, et al. Reduction in incidence of severe paracetamol poisoning. Lancet 2000; 355: 2047-48.

Prior MJ, Cooper K, Cummins P, Bowen D. Acetaminophen availability increases in Canada with no increase in the incidence of reports of inpatient hospitalizations with acetaminophen overdose and acute liver toxicity. Am J Ther 2004; 11: 443-452.

Robinson D, Smith AMJ, Johnston GD. Severity of overdose after restriction of paracetamol availability: retrospective study. BMJ 2000; 321: 926-927.

Sheen CL, MacDonald TM. Severity of overdose after restriction of paracetamol availability. BMJ 2001; 322: 553-2.

Szarfman A, Machado SG, O'Neill RT. Use of Screening Algorithms and Computer Systems to Efficiently Signal Higher-Than-Expected Combinations of Drugs and Events in the US FDA's Spontaneous Reports Database. Drug Safety 2002; 25:381-392.

Thomas MR, Jowett NI. Restriction has not reduced admission with self poisoning. BMJ 2001; 323: 633.

Turvill JL, Burroughs AK, Moore KP. Change in occurrence of paracetamol overdose in UK after introduction of blister packs. Lancet 2000; 355: 2048-2049.

Yoo Jung Chang, Pharm.D., Safety Evaluator

Concur:

Lauren Lee, Pharm.D., Safety Evaluator Team Leader

Parivash Nourjah, Ph.D., Epidemiologist

Syed Rizwanuddin Ahmad, M.D., M.P.H., Medical Epidemiologist

Concur:

Mary Willy, Ph.D., Epidemiologist Team Leader

Appendix 1. Top 10 drugs associated with OSE MedDRA grouping All Liver Events, stratified by year.[4]

MedDRA grouping: All Liver Events					
Cumulative	**2002**	**2003**	**2004**	**2005**	**2006**
APAP (5,564)	Cerivastatin (729)	Cerivastatin (2543)	**APAP** (691)	Rofecoxib (1177)	Rofecoxib (1465)
Lamivudine (4,942)	Lamivudine (690)	Bosentan (653)	Bosentan (572)	**APAP** (848)	**APAP** (511)
Troglitazone (4,341)	Stavudine (522)	**APAP** (576)	Atorvastatin (568)	Atorvastatin (618)	Lamivudine (404)
Rofecoxib (4,291)	**APAP** (470)	Lamivudine (544)	Rofecoxib (556)	Atomoxetine (536)	Telithromycin (403)
Cerivastatin (4,284)	Atorvastatin (453)	Infliximab (415)	Infliximab (543)	Lamivudine (534)	Duloxetine (382)
Atorvastatin (3,405)	Zidovudine (432)	Atorvastatin (404)	Lamivudine (497)	Ribavirin (477)	Atorvastatin (350)
Stavudine (3,073)	Didanosine (392)	Zidovudine (363)	Leflunomide (435)	Interferon beta 1a (473)	Isotretinoin (328)
Zidovudine (3,007)	Infliximab (379)	Stavudine (360)	Ezetimibe (397)	Ritonavir (445)	Ritonavir (302)
Simvastatin (2,879)	Troglitazone (363)	Ezetimibe (342)	Methotrexate (347)	Olanzapine (440)	Simvastatin (271)
Ritonavir (2,496)	Simvastatin (355)	Simvastatin (330)	Ritonavir (342)	Simvastatin (403)	Ribavirin (269)

Appendix 2. Top 10 drugs associated with OSE MedDRA grouping Liver Failure, stratified by year.[4]

MedDRA grouping: Liver Failure					
Cumulative	**2002**	**2003**	**2004**	**2005**	**2006**
APAP (2,056)	**APAP** (167)	**APAP** (212)	**APAP** (232)	**APAP** (300)	Rofecoxib (1465)
Troglitazone (1,298)	Troglitazone (166)	Lamivudine (98)	Lamivudine (105)	Ribavirin (142)	**APAP** (511)
Lamivudine (1,021)	Lamivudine (156)	Rosiglitazone (89)	Rosiglitazone (105)	Atorvastatin (116)	Lamivudine (404)
Stavudine (630)	Stavudine (131)	Ribavirin (82)	Rofecoxib (77)	Lamivudine (100)	Telithromycin (403)
Nevirapine (560)	Nevirapine (94)	Stavudine (64)	Gabapentin (75)	Ritonavir (90)	Duloxetine (382)
Didanosine (466)	Didanosine (86)	Pioglitazone (54)	Ribavirin (75)	Peginterferon alfa 2a (71)	Atorvastatin (350)
Ribavirin (459)	Atorvastatin (74)	Infliximab (53)	Infliximab (73)	Infliximab (66)	Isotretinoin (328)
Atorvastatin (434)	Cerivastatin (65)	Ritonavir (52)	Atorvastatin (71)	Peginterferon alfa 2b (66)	Ritonavir (302)
Methotrexate (417)	Efavirenz (61)	Didanosine (52)	Interferon beta 1a (58)	Rofecoxib (65)	Simvastatin (271)
Ritonavir (412)	Ribavirin (61)	Oxycodone (51)	Methotrexate (54)	Cyclophosphamide (65)	Ribavirin (269)

Appendix 3. Summary of Studies Related to Acetaminophen (APAP) Risk Minimization Strategies to Decrease Overdoses (OD)

#	Study	Year	Location	Outcome	Findings	Comments	Author's Summary
1	Prince et al, 2000	Compare Oct 1995 to Sep 1998 to Sep 1998 to Dec 1999	UK	Records from one liver unit and the UK liver transplantation list	• Median number of monthly referrals to liver unit fell from 2.5 to 1 ($p<0.02$) • Monthly number of referrals to transplant list fell from 3.5 to 2 ($p<0.02$) • Severity level unchanged	Poulin says no evidence for causality; no breakdown by intention or mortality; what about other drugs, do they increase?	"We report a reduced rate of severe APAP hepatotoxicity both locally and nationally, which coincides with decreased availability"
2	Turvill et al, 2000	Records Sep 1995 to Aug 1999	UK	Records of overdoses presenting to one hospital	• 21% decrease in cases of APAP OD; 64% reduction of severity (require N-acetylcysteine) • Save 200 inpatient days • Percent of benzodiazepine OD (expressed as % of all other OD) stable	See above	"The findings of this audit suggest a significant change in OD after introduction of blister packs" Note: Other drugs (benzos) not changed
3	Robinson et al, 2000	Compare Jan to Jun 1998 to Jan to Jun 1999	Northern Ireland	Patients presenting to 5 hospitals with acute self poisonings	• Serum concentration decreased ($p=0.003$); 37 mg/l to 27 mg/l • Number admitted did not change significantly; 398 to 374 • 2 patients referred to tertiary center in 1998; 3 in 1999	Sheen et al says we need stricter definitions of overdose since median serum concentrations in this study are low.	"We conclude that measures to restrict availability of APAP have reduced the amount taken in single OD, but not the incidence of severe liver failure."

	Study	Year	Location	Outcome	Findings	Comments	Author's Summary
4	Thomas, et al 2000	Compare Feb to Aug 1998 (N=116) and Feb to Aug 1999 (N=112)	UK	Admissions for OD at one hospital	• Number of APAP OD decreased; 52 (45% of all OD)) to 40 (36%) • 30 (68%) took more than 16 tabs before compared to 18 (51%) after legislation • Non-APAP increased; 64 to 72 cases • Time in hospitals same for both periods	Author: may have less liver transplant unit needs, but still need hospital care	"Our results suggest that patients are now switching to alternative agents… there may be less demand for liver units, but the unwanted workload for general physicians is the same." Note: number of other drugs increased
5	Hawton et al, 2001 (see updated study below)	Databases from 1996 to 1999	UK	England and Wales mortality data (Sep 1996 to Sep 1999); liver transplantations and listings from 5 units (Oct 1996 to Sep 1999); non-fatal poisonings presentations at 7 hospitals (Sep 1997 to Sep 1999)	• Decreased numbers of deaths; 21% for APAP and 48% for ASA • Number of liver unit admissions decreased 30% • Number of APAP non-fatal poisonings deceased 11% • Percent OD with >32 tabs decreased 17% • Significant increase in OD with APAP compounds in 4 of the hospitals (Author says maybe b/c of decreased availability of APAP)	Dargan et al: period of study is too short	"Legislation restricting pack sizes of APAP and ASA has had substantial beneficial effects on mortality and morbidity associated with self poisoning using these drugs."

	Study	Year	Location	Outcome	Findings	Comments	Author's Summary
6	Balit C et al, 2002	Compare Mar to May and Jun to Aug 1997-1999 compared to Mar to May and Jun to Aug 2000; study recall effect	Western Australia	Calls to poison control center and presentations to Toxicology Service	• No significant change in APAP or ASA calls over total recall; but was a non-significant decrease in APAP calls in the first recall period • Saw significant increase in ibuprofen calls and ASA presentations		"Reduced APAP availability increased poisonings for alternative analgesics, but had little effect on the incidence APAP poisonings."
7	Hughes et al, 2003	Apr 1995 to Jan 2003	UK	Admissions to two hospitals with APAP OD (1 hospital) and number admitted to liver unit (1 hospital)	• 31% decrease in number of patients admitted to hospital (average 360 to 250 per year) • 50% decrease in admission to liver units (average 76 to 38 per year)	Author: decrease in liver unit admissions may be due to staffing shortages. May also see decrease in pediatric deaths	"Legislation restricting APAP pack-size reduced the incidence and severity of poisoning."
8	Kisely et al 2003	1996 to 2001: Australian recall Mar 16 to May 21, 2000 (146 days)	Western Australia	Poisoning admission rate in WA; use WA population for denominator and time series analysis	• Significant decrease in admission rate (p=0.01) • Also decrease for ibuprofen or ASA or other drugs; all rates decreased. • Weekly time series analysis found non significant decrease in APAP admissions	Author: admissions for APAP OD showed large random variation that tended to obscure any effect	"Limiting access to APAP may reduce APAP poisonings without an coincident increase in the use of other agents."

	Study	Year	Location	Outcome	Findings	Comments	Author's Summary
9	Hawton et al, 2004	Databases from 1993 to 2002	UK	England and Wales mortality data (1993 to 2001); liver transplantations and listings from all but 1 unit in England and Scotland (1996 to 2002); non-fatal poisonings presentations at 5 hospitals (1997 to 2001)	• Deaths (suicide, open verdicts and accidental) for any APAP or ASA decreased 22% • 30% decrease in admission to liver units for APAP OD and also 30% decrease for transplants • 15% decrease in APAP presentations to hospitals in first year but not after; number of ibuprofen increased by 27% in 2nd and 3rd year but mortality was not greatly affected (11 to 13 deaths) and other drugs were involved. • OD > 32 tabs decreased significantly in years 2 and 3 for APAP and ASA, not ibuprofen		"Legislation restricting pack sizes of analgesics has been beneficial." Note: Ibuprofen OD increased, but with little effect on death.
10	Prior, et al 2004	Apr 1995 to Mar 2001; follows lifting of place-of-sale restrictions on APAP that allowed the sale of all strengths of IR APAP (had been limit of >325 mg and all packages of	Canada	Canadian hospital discharge data	• Compared rates (used population as denominator) and found no significant change • **Of note** the rates were consistently higher for the provinces that never had an acetaminophen restriction policy regardless of time period.	Author comments that may be too early to analyze.	"The decision to lift Canadian place-of-sale restrictions increased APAP availability and did not increase the rate of reported hospitalizations related to APAP OD."

	Study	Year	Location	Outcome	Findings	Comments	Author's Summary
		>24 tablets)					
11	Bateman, et al 2004	1995 to 2004	Scotland	In-hospital deaths (1995 to 2004) and hospital discharges (1995 to 2003) for Scotland	• Majority of deaths were due to co-proxamol • Proportion of deaths related to APAP was higher after legislation • Overall the number of poisonings fell post legislation but those involving APAP in any form decreased for <20 years and increased for those over 20 years		"Legislations have not reduced mortality or proportional use of APAP in OD, both of which appear to have increased in Scotland since pack-size limitations."

Department Of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Nonprescription Products
Division of Nonprescription Clinical Evaluation

Nonprescription Drug Clinical Review

Acetaminophen-Induced Hepatotoxicity

Subject	Acetaminophen-induced hepatotoxicity
Active Ingredients	Acetaminophen (APAP)
Indication	Temporary relief of minor aches and pains and temporary reduction of fever
Target Population	Individuals ages six months and older
Dosage/Route of Administration	Children less than 12 years of age: 10 – 15 mg/kg Individuals 12 years and older: 650-1000 mg Q4-6 hrs up to 4 g/day
Review Completion Date	March 8, 2007
Review Content	Data on acetaminophen-induced hepatotoxicity from 2002 – 2006 Regulatory and educational options to mitigate this risk
Reviewers	Karen B. Feibus, M.D. Steven Osborne, M.D.

Table of Contents **Page**

Introduction

Data from a large national survey suggest that 36% of Americans ingest an acetaminophen-containing compound at least once a month.[1] Compared with the millions of acetaminophen tablets consumed by Americans each day, the incidence of acute liver failure (ALF) due to acetaminophen is low. However, use of twice the recommended daily dose for a few days causes severe liver failure and death in some individuals. Acetaminophen (APAP) has been the number one cause of drug-induced liver failure in children and adults since at least the 1990's[2], but in 2005, APAP became the number one cause of acute liver failure in the United States.[3] The purposes of this paper are to:

- Review the published data on acetaminophen-associated hepatotoxicity in adults and children from 2002 to 2006
- Present regulatory and educational options that may reduce the unintentional (and possibly intentional) overuse and abuse of acetaminophen-containing products that can lead to hepatotoxicity and its associated morbidity and mortality.

Intentional overdose with APAP has a well-characterized risk of hepatotoxicity, liver failure, and possible death. The International Classification of Diseases categorizes acetaminophen overdose as "clearly intentional acetaminophen overdose" with intent of suicide or self-inflicted injury and as "not clearly intentional acetaminophen overdose", which apparently includes any other cause of acetaminophen overdose. During the past decade, recognition and concern about APAP-associated hepatotoxicity associated with acute or chronic overdosing with therapeutic intent has grown. Pediatric and adult patients with unintentional APAP overdose pose a greater diagnostic challenge, as they often develop symptoms subtly over a longer period of time and present with more advanced hepatotoxicity than those with an acute intentional overdose. Either acute or chronic unintentional overdose may include multiple APAP-containing drugs, increasing the risk of hepatotoxicity. Kearns et al. commented that *acetaminophen overdose with therapeutic intent constitutes a toxicologic entity distinct from acute intoxication in both its presentation and epidemiology*.[4] However, the literature does not specify whether an acetaminophen overdose due to deliberate ingestion of more than the recommended dose, with therapeutic intent, should be classified as an intentional or unintentional overdose. For this review, unintentional overdose refers to accidental poisoning and any overdose in which suicide or self-inflicted injury was not the goal.

Acetaminophen: Regulatory History

In 1960, FDA approved a new drug application for the over-the-counter (OTC) marketing of a 325 mg immediate-release tablet formulation of APAP for the following indications:

> *The temporary relief of minor aches and pain associated with the common cold, headache, toothache, muscular aches, backache, for the minor pain of arthritis, for the pain of menstrual cramps and for the reduction of fever.*

On July 22, 1975, FDA approved NDA 17-552 for Extra Strength Tylenol 500 mg APAP immediate release tablet with a maximum daily dose of 4 g. Superior efficacy of the 1000 mg

dose of APAP versus the 650 mg dose of APAP was supported by two clinical studies in women with post-episiotomy pain.

As part of the OTC Drug Review process, the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Products recommended APAP as a Category I analgesic product and expressed concerns about the public not regarding OTC products as medicines that can *result in injury or potentially serious consequences* and stated that the public needs to know that all medicines carry some risk and should be treated with respect (42FR35346, ANPR 07/08/1977). The Panel recommended that all products containing acetaminophen contain the following liver warning: *Do not exceed recommended dosage because severe liver damage may occur (42FR35355).*

A Proposed Rule (PR) for Internal Analgesic Products published on November 16, 1988 (53FR46204). After review of many comments that opposed organ-specific label warnings on analgesic products, FDA decided to omit the Panel's recommended liver warning for acetaminophen from the PR. However, FDA acknowledged that it was appropriate to warn consumers of potential drug toxicities associated with use of an OTC drug and that it may be necessary to include organ-specific warnings.

Table 1 displays the current indications and durations for use for nonprescription acetaminophen-containing products as described in the 1988 PR.

Table 1: OTC Acetaminophen Indications and Durations for Use

Population	Indications	Duration of Use
Adult (12 years and older)	For the temporary relief of minor aches and pains associated with the common cold, sore throat, headache, toothache, muscular aches, backache, premenstrual and menstrual cramps, the minor pain from arthritis, and to reduce fever	3 days for fever 10 days for pain
Children (2 years to under 12 years of age)	For the temporary relief of minor aches and pains associated with the common cold, sore throat, headache, toothache, and to reduce fever	3 days for fever 5 days for pain

The PR included a dosing range based upon age, but did not include dosing for children younger than age two years or dosing based on weight. However, as found in the 2007 Physician's Desk Reference (PDR) for Nonprescription Drugs, Dietary Supplements, and Herbs, acetaminophen is currently marketed with dosing that includes children younger than two years of age and dosing by weight[75]. Thus, Tables 2 and 3 display dosing schemes for currently-marketed adult and pediatric acetaminophen products[75].

Table 2: Dosing for APAP Non-chewable Tablets		
Product	**Age**	**Dose**
APAP 325 mg	Under 6 years	Do not use
	6 to 11 years	1 tablet every 4 to 6 hours as needed. Do not take more than 5 doses in 24 hours.
	12 years and older	2 tablets every 4 to 6 hours as needed. Do not take more than 12 tablets in 24 hours, or as directed by a doctor.
APAP 500 mg	Under 12 years	Do not use
	12 years and older	2 tablets every 4 to 6 hours as needed. Do not take more than 8 tablets in 24 hours, or as directed by a doctor.

Table 3: Dosing for APAP Concentrated Infant Drops and Children's Suspensions*			
Product	**Weight**	**Age**	**Dose**
APAP Concentrated Infant Drops (80 mg/0.8 mL)	6 to 11 pounds	0-3 months	½ dropperful (40 mg)
	12 to 17 pounds	4 to 11 months	1 dropperful (80 mg)
	18 to 23 pounds	12 to 23 months	1 ½ dropperfuls (120 mg)
	24 to 35 pounds	2 to 3 years	2 dropperfuls (160 mg)
APAP Children's Liquids	Under 12 pounds	Under 4 months	Consult a doctor
	12 to 17 pounds	4 to 11 months	½ teaspoon (80 mg)
	18 to 23 pounds	12 to 23 months	¾ teaspoon (120 mg)
	24 to 35 pounds	2 to 3 years	1 teaspoon (160 mg)
	36 to 47 pounds	4 to 5 years	1 ½ teaspoons (240 mg)
	48 to 59 pounds	6 to 8 years	2 teaspoons (320 mg)
	60 to 71 pounds	9 to 10 years	2 ½ teaspoons (400 mg)
	72 to 95 pounds	11 years	3 teaspoons (480 mg)

*manufacturer says to use weight if possible; otherwise use age. Also, take no more than 5 doses in 24 hours.

In September 2002, the Nonprescription Drugs Advisory Committee (NDAC) and members of the Office of Drug Safety (ODS, now the Office of Surveillance and Epidemiology, OSE) addressed unintentional overdose of acetaminophen and hepatotoxicity. FDA stated that acetaminophen should remain available OTC given its overall effectiveness and safety, the benefits that an OTC pain reliever/fever reducer offers to consumers, and its use by tens of millions of people each week. FDA noted factors that contribute to unintentional overdose and acetaminophen-associated hepatotoxicity:

- Acetaminophen is available to consumers in many OTC and prescription drug products
- Consumers fail to identify acetaminophen as an ingredient in their OTC and prescription drug products
- Consumers are not aware of the risks of exceeding the recommended dose or dosing frequency of acetaminophen-containing products or the risks of simultaneously using multiple acetaminophen-containing products.

Following discussion of data presented by FDA, industry, researchers, and the public, NDAC made the following recommendations:

- All products containing acetaminophen should be distinctively labeled (highlighted or bold) on the front panel or principle display panel with the name acetaminophen.
- On the OTC products, the committee recommended a liver toxicity warning separate from the currently required alcohol warning.[5]
- FDA and manufacturers should educate consumers and health professionals about the risk associated with ingesting too much acetaminophen and the occurrence of unintentional liver injury.
- The committee agreed with including dosing directions in children's products for children < 2 years of age.

Following the AC meeting, FDA Consumer Magazine summarized the advisory committee's recommendations in their January 2003 issue and presented information on unintentional acetaminophen-induced hepatotoxicity and non-steroidal anti-inflammatory drug-related gastrointestinal bleeding. FDA launched a consumer campaign on the safe use of OTC pain products in January 2004. This program included printed public service announcements (PSAs), a FDA Science Paper posted on the internet, and a letter sent to all fifty State Boards of Pharmacy that stressed the importance of clear-labeling of acetaminophen content on all dispensed prescription medicines containing acetaminophen. Based on advisory committee recommendations, the Division of Over-the-Counter Drug Products (now the Office of Nonprescription Products, ONP) drafted a proposed rule requiring an organ specific liver warning and a size-specified, prominent appearance of the word "acetaminophen" on the principal display panel for all acetaminophen-containing nonprescription drug products. This document was published on December 26, 2006.

On December 4-5, 2006, the National Institutes of Health (NIH) hosted a meeting on Acute Liver Failure. The objectives of the meeting were to convene experts on and assess current knowledge about acute liver failure: its causes, incidence, natural history, management, and prevention. A portion of the meeting focused on APAP hepatotoxicity. Relevant, but as yet unpublished, information shared at the meeting is integrated into this options paper where appropriate.

Acetaminophen: Mechanism for Hepatotoxicity and Concomitant Risk Factors

The mechanisms of APAP toxicity and concomitant risk factors that may predispose to toxicity are presented in Appendix A at the end of this paper.

Acetaminophen-Induced Hepatotoxicity in Adults

Although intentional APAP overdose has been a public health problem and a recognized cause of liver failure in the United Kingdom since the 1970's, APAP was not mentioned as a cause of acute liver failure (ALF) in the United States until the 1980's. A U.S. retrospective study from 1994-1996 found that 20% of ALF cases are caused by acetaminophen toxicity. The majority of reports involve intentional APAP overdose, but cases of APAP-associated hepatotoxicity from unintentional overuse for treatment of pain and hepatic injury following therapeutic doses also appeared in the literature.

In preparation for the September 2002 AC, FDA reviewers from the Office of Drug Safety reviewed APAP-associated hepatotoxicity data from national databases and the FDA Adverse Event Reporting System (AERS) to estimate the public health impact of hepatotoxicity in the United States. This information is presented below. This data is followed by summaries of published studies from 2002 – 2006, including the first two studies published by the U.S. Acute Liver Failure Study Group (US ALFSG). In 1997, this consortium of liver centers formed to better define the causes and outcomes of ALF and to compare presenting clinical features and liver transplantation rates between patients with ALF related to APAP overdose and those with ALF due to other drugs, causes, or indeterminate factors.

FDA Summary of Population Database Information on Acetaminophen-Associated Hepatotoxicity (1990 – 2001)

Drs. Nourjah, Ahmad, Karwoski, and Willy, reviewers from CDER's OSE, published a study presenting national estimates of APAP-associated overdoses obtained by analyzing national databases.[6] The authors used six different surveillance systems that included data from emergency departments (EDs), hospital discharges, mortality data, poison control centers, and spontaneous postmarketing adverse drug event reports reported to the Food and Drug Administration (FDA). Among the six surveillance systems listed below, the first three are national surveys that use probability sampling. Additional details about these information sources may be found in Appendix B.

- National Hospital Ambulatory Medical Care Survey (NHAMCS)
- Consumer Product Safety Commission's National Electronic Injury Surveillance System All Injury Program (NEISS)
- National Hospital Discharge Survey (NHDS).
- National Multiple Cause of Death File (mortality files)
- Toxic Exposure Surveillance System (TESS)
- FDA Adverse Event Reporting System (AERS)

Findings from this study were presented and discussed at the September 2002 NDAC and are summarized in the Key Data Points window below. A detailed review of Nourjah et al's 2006 publication is provided in Appendix B.

Key Data Points
56,000 Emergency department visits and 26,000 hospitalizations per year for APAP associated overdose – 63-69% female.
About 458 deaths per year (in 1990's) caused by or contributed to by APAP – 58% female.
Unintentional overdose probably accounts for about 25% of cases (8% NHDS, 22% Cause of death files, 23% ED data, 26% TESS, 41% AERS)
Most APAP overdoses involve the use of one APAP product but 10 – 26% involved the use of two or more products, often an OTC and a RX product.
Toxicity, including death, occurred with mean daily doses less than twice the maximum recommended daily APAP dose of 4 g/day. Up to 30% of individuals with APAP toxicity reported to AERS took 4g/day or less.

Comment:
FDA AERS database crude counts for acetaminophen-associated deaths in 2004, 2005, and 2006 suggest that cases of acetaminophen-associated hepatotoxicity and death are not declining. However, these data should be viewed with caution since multiple drugs may have been listed as associated with the death and the role of acetaminophen may be unclear.

Other Published Data on Acetaminophen-Associated Hepatotoxicity in Adults

Gyamlani and Parikh (2002)
When Gyamlani and Parikh[7] published their February 2002 study report on APAP toxicity, APAP was the second leading cause of toxic drug ingestion in the United States (it is now the first). Their objective was to describe the epidemiology of various types of APAP poisoning and analyze their outcomes in an urban county hospital (East Meadow, NY). The authors identified all admission records from January 1996 – April 1999 with a discharge diagnosis of APAP overdose. Patients evaluated or treated in the emergency room, who were not admitted to the hospital, were excluded from the study. The authors reviewed the medical records and confirmed APAP ingestion by history (self or family), blood level (> 10 mg/L), or serum aminotransferase level > 1000 IU/L. Patients had to meet two out of these three criteria for inclusion. Chronic alcohol abuse was defined by the DSM- IV[8] criteria.

Reviewer comment:

1. *It is not clear whether the authors chose an APAP serum level of > 10 mg/L because this was the lower limit of detection for their laboratory or if they chose it for another reason.*

2. *The Rumack-Matthew nomogram estimates that a serum APAP level of 10 mg/L is possibly or probably toxic if the APAP was ingested more than 19 hours prior to the serum measurement (from Acetadote® Injection labeling approved 02/14/2006).*

3. *In the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV),* ***alcohol abuse*** *is defined as a maladaptive pattern of alcohol use leading to clinically significant impairment or distress, manifested in a 12-month period by one or more of the following problems: (1) failure to fulfill role obligations at work, school, or home; (2)*

recurrent use of alcohol in hazardous situations; (3) legal problems related to alcohol; and (4) continued use despite alcohol-related social problems.[9]

The authors identified one hundred eligible patients but excluded seven due to co-morbid conditions or clinical presentations unrelated to acetaminophen ingestion. APAP ingestion accounted for 7.5% of all hospital poisoning admissions during this time. Among the 93 eligible subjects, eighty (86%) were classified as suicidal based on psychiatric evaluation, and 13 (14%) were classified as accidental (unintentional) overdoses while seeking to relieve pain. Causes of pain included toothache, chronic backache, and headache. Mean peak serum APAP levels were higher in patients with intentional overdose (122 mg/L vs. 65 mg/L), but a greater percentage of patients with unintentional overdose had peak aminotransferase levels greater than 1000 IU/L (39% vs. 12%). Morbidity and mortality were higher in the unintentional overdose group. Two patients with unintentional APAP overdose developed ALF, hepatic coma, and died. One of these patients had a history of chronic alcohol abuse.

Patients with unintentional overdose ranged in age from 1 – 88 years with a median of 36 years (mean 35 years). Five of these patients were female and 10 were Caucasian. Five (38%) patients met the DSM-IV criteria for chronic alcohol abuse, and three (23%) were intoxicated at the time of presentation. By comparison, 18% of suicidal patients with acetaminophen overdose met the DSM-IV criteria for chronic alcohol abuse and 45% were intoxicated upon arrival at the hospital. Some patients in the unintentional overdose group were unaware that their over-the-counter drugs contained acetaminophen. Thirty-eight percent of patients with unintentional overdose had APAP levels less than 10 mg/L. These subjects met the other two study criteria for APAP overdose: substantial APAP ingestion by history and serum aminotransferase level > 1000 IU/L. The authors attributed the subjects' low APAP serum levels to late presentation and ingestion of smaller APAP doses over a longer period of time compared to their suicidal counterparts.

The authors noted that peak plasma APAP levels are unreliable in predicting hepatic dysfunction, especially in patients with accidental overdose. They recommended that patients with unintentional overdose should be considered for N-acetylcysteine treatment and that chronic alcohol abusers should be treated at APAP plasma levels half of those indicated in the standard graph. In addition, the authors noted that 75 of 80 patients with suicidal overdose and all 13 patients with unintentional overdose were admitted to the intensive care unit for one to two days at a cost of $25,000 – 35,000 per day (in 1999).

Ostapowicz et al, US ALFSG (2002)
Larson et al, US ALFSG (2005)

In December 2002, Ostapowicz et al[10] and the US Acute Liver Failure Study Group (ALFSG) published data on their first 308 patients with ALF. Hepatic coma was graded on a standard scale of I to IV. At each study center, etiologic diagnoses were based on accepted diagnostic criteria circulated to all investigators. These criteria incorporated: history, laboratory values, imaging studies, and histopathology characteristics in some cases. The cause of ALF was indeterminate when extensive clinical, radiographic, and laboratory evaluation (including toxicology screens and serologic markers for viral hepatitis A, B, and C and antinuclear and anti-smooth muscle antibodies) was inconclusive. Investigators used RNA testing methods to search

for other viral etiologies when clinically indicated, but results were not uniformly available. Clinical guidelines for patient management were uniform even though they were determined at each study site. Candidacy for liver transplantation was determined at each individual medical center according to the guidelines of the United Network of Organ Sharing.

Seventy-three percent of the subjects were female, and the etiologies for ALF were as follows: 39% APAP overdose, 13% idiosyncratic drug reactions, 7% Hepatitis B, 4% Hepatitis A, and 2% pregnancy associated liver failure (acute fatty liver, HEELP syndrome, eclampsia). Forty-two subjects had presumptive diagnoses of ischemic hepatitis, autoimmune hepatitis, Wilson's disease, and Budd-Chiari syndrome. Among subjects with APAP-associated ALF, 83% used more than the maximum daily recommended APAP dose of 4 g/day, but 17% used a daily APAP dose of 4 g or less. Half of the subjects with APAP-associated ALF overdosed accidentally.

This study was ongoing, and in 2005, Larson et al[11] reported on the subpopulation of 275 subjects with acetaminophen-associated ALF among 662 US ALFSG patients who enrolled between January 1, 1998, and December 31, 2003.

Demographic, clinical, laboratory, and outcome information were prospectively recorded for all subject meeting study entry criteria for ALF at the 22 participating academic centers. By definition, eligible subjects met the following criteria:

- INR ≥ 1.5
- Evidence of hepatic encephalopathy
- Presented within 26 weeks of illness onset without apparent chronic liver disease
- Written informed consent by legal next of kin.

Whenever possible, study staff obtained the following information on each patient's APAP ingestion: total dose, type of acetaminophen product used, and duration of use. To assign APAP ingestion as the cause of acute liver failure (ALF), a patient had to meet one or more of these criteria:

- History of potentially toxic APAP ingestion (> 4g/day) within seven days of presentation
- Detection of any serum level of APAP
- Serum alanine aminotransferase (ALT) > 1000 IU/L and a history of APAP ingestion.

In addition, study staff had to exclude other potential causes of ALF such as acute hepatitis A or B, hepatic ischemia, autoimmune hepatitis, Wilson disease, and hepatitis of other etiologies. The local site investigators assigned patients with APAP-related ALF to one of two groups:

- Intentional (suicidal) ingestion: a single time-point ingestion in a patient admitting suicidal intent
- Unintentional ingestion: a multiple time-point ingestion to relieve pain or other somatic symptoms with denial of suicidal intent.

The study defined alcohol abuse in terms of daily alcohol consumption: at least 40 g/day for men and at least 20 g/day for women.

Reviewer comments:

- *A standard drink in the United States contains 14 g ethanol. A standard drink in the United Kingdom and Australia contains 10 g ethanol. There are 42 g of ethanol in 3 standard U.S. drinks. There are 21 g of ethanol in 1.5 U.S. drinks.*[12]

- *Among subjects who used alcohol but did not meet the study definition for alcohol abuse, the authors did not distinguish between acute and chronic alcohol use or identify non-daily abuse (binging).*

Each center applied its own liver transplantation criteria to study patients admitted to that center. Study investigators reviewed all case report forms at the central study site (University of Texas, Southwestern Medical Center) to confirm subject diagnoses.

Among 662 ALF subjects enrolled in the study, 302 (46%) had APAP-related hepatotoxicity. On further review, the investigators excluded 27 of these subjects because there were insufficient data to rule out other causes or because co-existing clinical conditions may have contributed to the ALF (like viral hepatitis, poly-drug use, or shock). During each year of the study, acetaminophen was the most common cause of ALF and this percentage increased annually from 28% in 1998 to 51% in 2003. Idiosyncratic drug-induced hepatotoxicity was the second most common cause (12%) and the cause was indeterminate in 19% of subjects.

The final study group with APAP-associated hepatotoxicity included 275 subjects (42% of the 662 ALF subjects enrolled in the study). Seventy-four percent were female and this percentage was consistent among those with intentional and unintentional overdose. Subjects with APAP-related hepatotoxicity ranged in age from 17 to 76 years and in weight from normal to morbidly obese. Median body mass index (of 196 calculated) was in the normal range. The vast majority of subjects were Caucasian (88%) with African Americans comprising 5% of the study population. Hispanics, Asians, Native Americans, and other races each made up two percent or less of the population. One hundred fifty-five (56%) subjects met all three criteria for assigning APAP ingestion as the cause of ALF. Serum APAP levels were detectable in 212 (77%) subjects, and ALT was ≥ 1000 IU/L in 250 (91%) subjects.

Data Summary Points
662 cases of acute liver failure
275 cases APAP-associated
204 (74%) female
242 (88%) Caucasian
122 (44%) intentional overdose
131 (48%) unintentional overdose

(N=275 unless otherwise stated)
182 (66%) used an OTC APAP product
147 used only OTC APAP products
-141 (96%) used 1 OTC product
- 6 (4%) used 2 OTC products
120 (44%) used a Rx narcotic/APAP
- 76 (63%) used narcotic/APAP alone
- 41 (34%) used narcotic/APAP+OTC
47 (17%) used > 1 APAP product

151 (55%) used alcohol (N=273)
68 (35%) abused alcohol (n=196)
108 (39%) used an anti-depressant

79 (29%) died

Table 4 summarizes available clinical information about the study population as a whole and by overdose intent. One hundred twenty-two (44%) subjects reported an intentional overdose and 131 (48%) experienced an unintentional overdose without suicide intent. Intent was not clear in 8% of subjects. Compared to those attempting suicide, subjects with unintentional overdose were, on the whole, older (median 38 vs. 34 years), more likely to use multiple APAP-containing preparations (38% vs. 5%), and more likely to seek care longer after symptom onset (median 4 days vs. 1 day). These subjects were more likely to have severe hepatic encephalopathy (grades 3 or 4) at

Table 4: Features and Outcomes for Subjects With Acetaminophen-Related ALF (all measures of central tendency are medians)

Characteristic		All [N = 275]	Unintentional Overdose* [N = 131]	Intentional Overdose* [N = 122]
Age in years (age range)		37 (17-76)	38 (18-76)	34 (17-68)
Female gender (%)		204 (74%)	96 (73%)	90 (74%)
Body Mass Index (Normal = 19-25 kg/m^2)		-	25 (17-51) [N=97]	24 (16-56) [N=99]
Serum APAP level, µg/dL [N]		31 (0-644) [N=257]	18 (0-400) [N=119]	64 (0-644) [N=118]
APAP dose, g	Median Daily (range) [N]	-	7.5 (1.0-7.8) [N=77]	25 (1.2-90) [N=91]
	Median Total (range) [N]	-	20 (2.5-180) [N=81]	25 (1.2-90) [N=91]
Alcohol use		151 (55%) [N=273]	-	-
Alcohol abuse		68 (35%) [N=96]	-	-
OTC APAP product	1 product 2 products	141 (51%) 6 (2%)	-	-
APAP/narcotic product	Total Alone With OTC APAP	120 (44%)** 76 (28%) 41 (15%)	83 (63%)	22 (18%)
Anti-depressant use		108 (61%)	48 (37%)	46 (38%)
INR (Normal = 0.8-1.2)	Median (range) N(%) ≥ 3.0	3.0 (1.2-27.1)	56 (42%)	68 (56%)
Bilirubin, mg/dL	Median (range) N(%) ≥ 4	4.5 (0.3-48.2)	73 (56%)	74 (61%)
Serum ALT, IU/L	Median (range) N(%) ≥ 3500	4186 (136-19,826)	3319 (126-18,079) 63 (48%)	5326 (179-19,826) 88 (72%)
Serum creatinine	Median mg/dL (range) N(%) ≥ 2 mg/dL	2.0 (0.2-10.5)	74 (57%)	53 (43%)
Peak Hepatic Coma Stage 3 or 4		-	89 (68%)	72 (59%)
Hepatic coma grade on admission	1 2 3 or 4	84 (31%) 52 (19%) 135 (50%)	- - 72 (55%)	- - 47 (39%)
Liver Transplantation	Listed Received Days to Transplant	- - -	35 (27%) 12 (9%) 3 (1-7)	30 (25%) 8 (7%) 3 (2-5)
Overall outcome	Survived, no transplant Died, no transplant Transplant, lived 3 weeks Died, post-transplant	178 (65%) 74 (26%) 18 6%) 5 (2%)	84 (64%) - - -	80 (66%) - - -
Overall survival at 3 weeks		181 of 253 (72%)	94 (72%)	87 (71%)

*Type of overdose not known in 22 (8%) subjects.

** APAP/narcotic alone vs. with OTC APAP were unknown for 3 subjects.

admission but lower serum APAP levels than their suicidal counterparts. There were no other clinically significant differences between the two subject groups. Educational level was similar for the two groups and averaged 13.22 years for the population as a whole.

One hundred forty-one (51%) ALF subjects used one OTC APAP product alone, and six (2%) used two OTC APAP products. Among the 120 subjects who used a combination APAP/narcotic product, 76 (63%) subjects used the prescription product alone, and 41 (34%) used it in combination with an OTC APAP product. In total, concomitant use of more than one APAP-containing product contributed to liver toxicity in 47 (17%) subjects. Among users of APAP/narcotic combination products, 63% experienced unintentional APAP overdose and 18% reported an intentional overdose. The authors did not specify how many individuals using OTC APAP products alone experienced an unintentional versus an intentional overdose. All data shown is from the publication.

Information on alcohol use was available for 273 subjects of whom 55% used alcohol chronically (see comment after Table 4). Among the 196 subjects for whom actual alcohol intake was recorded, 35% met the criteria for alcohol abuse. Compared with non-abusers, alcohol abusers had lower APAP levels (median 15 µg/dL vs.34 µg/dL), were less likely to use anti-depressants (24% vs. 40%) or compound narcotics (31% vs. 50%, see comment below)), and were less likely to present with severe hepatic encephalopathy (34% vs. 53%). Seventy-seven subjects had toxicology screen results available, and 58 were positive. Half of these positive results were for illicit drugs (marijuana, cocaine, and amphetamines), and half were positive for potential drugs of abuse thought to represent prescribed medications (opiates, benzodiazepines, barbiturates, tricyclic antidepressants).

Comments:

- *The authors do not define chronic alcohol use or distinguish it from occasional use.*

- *It is important to remember that the definition of alcohol abuse for this study is three standard U.S. drinks per day for a male and 1.5 standard drinks per day for a female. Most people in American society do not consider this amount of alcohol intake to constitute abuse. This study suggests that the alcohol warning on APAP labeling should reflect a gender difference.*

- *The authors use the term "compound narcotics" in the paragraph above. This term apparently refers to a combination narcotic-acetaminophen product.*

Sixty-one percent of subjects used at least one anti-depressant, and anti-depressant use occurred with equal frequency among subjects with unintentional and intentional APAP overdose. Individuals using anti-depressants were, on average, older (median 39 yrs) and more likely to use prescription APAP/narcotic combination products (55% vs. 37%) and more likely to use additional prescription narcotics (17% vs. 5%).

Nineteen (7%) subjects reported taking 4 g of APAP per day or less prior to presentation: 14 experienced an unintentional overdose; 16 had ALT levels greater than 1000 IU/L; and 12 had measurable APAP serum levels. Seventy-nine percent of these individuals used alcohol and 65% with alcohol consumption data met the criteria for alcohol abuse. For comparison, subjects who

consumed more than 4 g/day APAP had a 37% prevalence of alcohol abuse. This difference was statistically significant.

Among those with unintentional overdose, 81% reported a cause of pain for which they used the APAP-containing drug. These reports included: chronic pain, chronic back pain, headache, chronic abdominal pain, viral upper respiratory infection, migraine, toothache, orthopedic pain, fibromyalgia, rheumatologic pain, chronic pancreatitis, and postsurgical pain. Nineteen (15%) of 131 subjects with unintentional overdose reported using acetaminophen for more than seven consecutive days. This group differed from subjects using acetaminophen for fewer than seven days in the following ways: older, greater weight, more likely to report pain as the reason for drug use, more likely to use additional narcotics, less likely to use alcohol.

Among 72 (26%) subjects listed for liver transplantation, 20 died, 29 recovered without transplant, and 23 (8%) underwent transplantation. Seventy-nine (29%) subjects died within three weeks of admission: 74 without transplantation and five following transplantation. Seventy-two percent of subjects with unintentional overdose and 71% of subjects with intentional overdose survived until three weeks post-admission. Individuals who used APAP chronically and those who acutely ingested an overdose exhibited the same type of acute liver injury and clinical presentation.

The authors noted the recent increase in the percentage of acute liver failure cases associated with APAP use and estimated that at least 250 APAP -related ALF cases and 73 deaths occur annually at transplant centers in the United States. This number does not account for APAP-related hepatotoxicity cases cared for at non-transplant centers and is less than the 458 APAP-related deaths per year predicted by FDA's Office of Drug Safety in 2002 based on an adverse event data review. Fifty percent of individuals developed hepatotoxicity and encephalopathy from unintentional overdose. The authors identified the following factors as potential contributors to unintentional APAP overdose scenarios:

- Repeated dosing in excess of package labeling
- Use of multiple acetaminophen-containing products
- Simultaneous use or abuse of alcohol and narcotics
- Chronic pain conditions
- Depression.

The authors suggest that drug regulatory changes in the United States may be needed to reduce the incidence of APAP-induced hepatotoxicity (limiting OTC package size, physically separating the narcotic and APAP components of combination prescription products, education for healthcare providers and consumers).

The authors noted the following strengths and limitations of their study. Strengths included representation of 30% of the U.S. transplant capability, evaluation of all subjects by experienced hepatologists, and inclusion of only the 60% of cases with informed consent and adequate data to ensure the diagnosis. The authors acknowledged that the study population may not represent the true incidence of ALF in the population as a whole since many patients are not referred to

transplant centers. In addition, medical history taking is difficult in patients with altered mentation.

Editorial comments published in response to the two US ALFSG articles described the eligibility criteria and definitions of APAP-associated hepatotoxicity as subjective and inaccurate respectively.[13] The comments raised concerns about whether subjects who consumed ≤ 4 g/day APAP really had APAP-associated hepatotoxicity.[14] A series of questions regarding the study data prompted a detailed response from William Lee, US ALFSG member that published in July 2004. Dr. Lee acknowledged that figures from the ALSFG studies on APAP-associated hepatotoxicity could not be equated with actual incidence figures; however, the documented increase in the percentage of ALF cases attributable to acetaminophen is striking. In addition, he noted that there is a difference between all patients entering the hospital with presumed APAP overdose and the small percentage of them who develop ALF. The US ALFSG only admits patients who develop coagulopathy and encephalopathy. For comparison, Parkland Memorial Hospital admitted 71 APAP overdose patients in a 39-month period but only seven patients developed acute hepatic failure and died. One patient died among the fifty who were considered suicidal, whereas six patients died among 21 with unintentional overdoses. [15] In his July 2004 publication, Dr. Lee also noted the recent development of an assay that reliably detects acetaminophen-containing protein adducts released into the plasma by dying hepatocytes. The assay allowed confirmation of unrecognized acetaminophen toxicity in 20% of ALF patients previously classified with liver failure of undetermined etiology. In the Ostapowicz study, 20% of patients with established viral hepatitis had detectable APAP serum levels. Compared to viral hepatitis patients without detectable APAP levels, these patients had significantly higher median ALT levels (5400 IU/L vs. 1367 IU/L). Although these patients were not considered APAP-associated ALF cases in the study, the use of APAP in the presence of chronic hepatitis may have contributed to the patients' acute morbidity.

Reviewer comment:

- *At the December 4, 2006, NIH Acute Liver Failure workshop, Laura James, M.D. presented unpublished data from her laboratory and the U.S. ALFSG showing that serum protein adducts strongly correlate with elevations of hepatic transaminases and are detectable in serum up to 10 days following severe APAP overdose. She also stated that recent modifications in the high-performance liquid chromatography-electron capture assay increased the sensitivity and efficiency of the test.*[16]

- *Unpublished data addressing APAP protein adducts in ALF patients with hepatitis are discussed in the next reviewer comment.*

Two editorial comments published in response to the Larson et al article raised concerns about the definition of cases of unintentional APAP overdose. Holubek et al stated that the exclusion criteria did not specifically include Hepatitis C, hepatotoxic drug exposure, or viral etiologies. Also, any person accompanying the patient could have provided a history of a multiple time-point APAP ingestion to relieve pain or other somatic symptoms with denial of suicidal intent. They felt that this presented a large recall and selection bias.[17] John G. O'Grady acknowledged that Larson et al adopted a broader set of diagnostic criteria for APAP-related hepatotoxicity and stated that only 40% of the patients fulfilled a more conventional definition of having a clear

history of taking APAP in excess, having detectable APAP serum levels, and having markedly raised transaminases. While these broader criteria almost *certainly resulted in the inclusion of some cases that were not truly related to acetaminophen use*, he felt that the credibility of the study results were supported by the remarkable similarity between the typical patients with acknowledged overdoses and the group whose disease was attributed to the therapeutic use of misuse of APAP. Other than having a median age six years older, the two groups were very similar with regards to demographics, natural history, and outcome.[18]

O'Grady suggested that the diagnostic criteria for APAP-related hepatotoxicity should be loosened and that the burden of proof for establishing the diagnosis should be lower than that used in the past. Although Larson et al concluded that ALF patients with a history of therapeutic use of APAP reach a point where they become acutely susceptible to liver injury (rather than representing a variant of acetaminophen liver injury with a more protracted pathogenesis), O'Grady states that that possibility of dual pathology in these patients should be considered given the likelihood that APAP will be used therapeutically in patients with viral illnesses. APAP is a significant co-factor in the pathogenesis of ALF in patients with acute Hepatitis B and those using anti-tuberculosis drugs.

Reviewer comment:

- *At the December 4, 2006, NIH Acute Liver Failure workshop, Julie Polson, M.D. presented unpublished data on protein adducts in hepatitis patients. The protein adduct assay conducted in Dr. James' lab detected acetaminophen adducts in sera from more than 12% of ALFSG patients with acute liver failure confirmed to have hepatitis A or B. Most of these patients reported using APAP at recommended doses to treat their symptoms of fever, myalgias, arthralgias, and headache. Hepatitis patients with positive adducts had 67% mortality at three weeks compared to 27% mortality in those without adducts. Dr. Polson stated that adduct levels in hepatitis patients were lower than those seen in patients with primary APAP-induced ALF but still suggest that ingestion of APAP likely contributed to liver injury.*[19]

While the work of the US ALFSG provides the most extensive and prospective data on APAP-associated ALF in the United States, data from Australia offers some similar findings regarding the occurrence of unintentional acetaminophen overdose. Unlike the United Kingdom where the vast majority of APAP overdoses are believed to represent suicide attempts or gestures, researchers from Australia have identified cases of unintentional acetaminophen overdoses that resemble those in the United States.

Gow et al (2004)

Gow et al[20] published a database review in 2004 that included patients 16 years and older who were referred to the one transplant center in Melbourne between 1988 and 2001. Among 80 patients (80% female) referred to the transplant center for ALF, 29 (36%) had APAP poisoning and 24 (83%) were female. Nine of the 29 patients had an unintentional overdose, and all of these accidental overdoses involved taking regular APAP over a period of several days for the treatment of pair or febrile illness. The authors reviewed the case histories for these patients and found that all nine had poor dietary intake during the period of APAP ingestion, and five had a history of long-term, excessive alcohol intake. Patients with APAP-associated ALF were listed

for transplantation only if they developed coagulopathy or cerebral edema (encephalopathy). The authors estimated that the rate of referral to the Victorian Liver Transplant Unit was about one case per million population per year but did not provide comparisons to other liver transplant centers in Australia. Consistent with data from the United States and the United Kingdom, the authors found that the vast majority of patients with APAP-induced ALF survived without transplantation. They did not provide data about amount of APAP ingested and did not differentiate outcomes for patients with intentional and unintentional overdose.

Reviewer comment:

- *The data from Gow et al (2004) and the data from Larson et al (2005) suggest that ALF due to intentional and unintentional APAP overdose is more common in women. At the December 4-5, 2006, NIH workshop on Acute Liver Failure, Anne Larson, M.D. stated that the U.S. ALFSG patient data were analyzed by body mass index to look for an association between body mass, gender, and outcome. No association was found. It should be noted, however, that the ALFSG study population is limited to individuals with ALF and encephalopathy. In order to determine whether smaller body mass contributes to a greater number of APAP-associated ALF cases among women than men, multiple comparisons should be considered:*
  - *Differences in number of males and females using APAP products*
  - *Differences in use patterns among males and females*
  - *Differences in BMI among female APAP users with acute or chronic overdose/overuse who do and do not develop ALF.*

Ayonrinde et al (2005)

In 2005, Ayonrinde et al[21] published a retrospective observational study of patients with APAP overdose admitted between January 2000 and December 2003 to a regional hospital in Victoria Australia. The authors reviewed the medical records of 188 of 192 patients who presented to the hospital after an APAP overdose. Patients were excluded if they consumed less than 2 g APAP by history or if paracetamol levels were undetectable. The authors classified nine cases as unintentional overdoses. These individuals used APAP for analgesia to treat toothache, back pain, or abdominal pain and consumed quantities of APAP similar to those consumed intentionally by other patients. No cases of hepatotoxicity resulted from a therapeutic dose of APAP. Twenty-six (14%) of patients with APAP overdose developed elevated ALT, four developed coagulopathy, and one developed encephalopathy, and six (3%) developed severe hepatotoxicity. The authors do not state how many patients with unintentional overdose developed hepatic injury, and American data suggest that individuals with unintentional overdose often have a more severe clinical course than those with intentional overdose.

Reviewer comment:

- *The authors did not specifically define "unintentional overdose." International Classification of Diseases -10 codes were used to identify patients with APAP overdose. Codes utilized included: intentional self-harm; analgesics, antipyretics and antirheumatics; poisoning by non-opioid analgesics, antipyretics, and antirheumatics; accidental poisoning by and exposure to noxious substances; and event of undetermined intent.*

Watkins et al (2006)
In this study, Watkins et al[22] demonstrated that some normal healthy volunteers who used APAP 1000 mg Q6 hours either alone or in combination with oxycodone, hydromorphone, or morphine sulfate for 14 days developed elevated liver transaminases. The authors conducted this study after they stopped a drug development trial early due to a high incidence of ALT elevations in subjects receiving the combination APAP/hydrocodone product under development. Subjects received four grams APAP per day. One hundred forty-seven healthy men and women, ages 18 – 45 years participated in this randomized, single-blind, placebo-controlled, parallel-arm, two-center study. Each subject was randomized to one of five study treatments in a 1:1:1:1:1.5 ratio:

- 2 tablets Percocet (7.5 mg oxycodone/500 mg APAP) + 2 tablets placebo
- 2 tablets Dilaudid (2 mg hydromorphone0 + 2 tablets 500 mg APAP
- 2 tablets 15 mg morphine sulfate + 2 tablets 500 mg APAP
- 2 placebo tablets + 2 tablets 500 mg APAP
- 2 placebo tablets + 2 placebo tablets

Subjects were housed in a clinical facility for the duration of study participation and received their study treatment every six hours for up to 14 days. Among subjects receiving placebo, 3% had ALT levels that reached two times the upper limit of normal, and no subjects had levels that reached three times the upper limit of normal. Among subjects in the four active treatment arms, 19% had ALT levels that reached five times the upper limit of normal. When peak ALT elevations were normalized by baseline values, 3% of placebo users had a peak ALT level more than five times their baseline value but 27% of active treatment subjects had a peak ALT level more than eight times their baseline value. There were no meaningful differences in the magnitude or incidence of elevated ALT among subjects in the different active treatment arms; however, there was a statistically significant difference between the placebo treated group and all of the active treatment groups with regard to ALT elevations. Exposure to any APAP was the single best predictor of elevated ALT response. All subjects remained asymptomatic.

Except for one subject in the morphine group and one in the APAP alone group who were lost to follow-up on Study Day 19, the abnormal ALT values remained elevated for a few days following cessation of treatment and then rapidly fell back into the normal range. Compared to non-Hispanic Americans, Hispanic Americans were nearly twice as likely to have a maximum ALT more than three times the upper limit of normal (RR = 1.9, 95% CI 1.1 – 3.3). There were no differences in mean APAP troughs, peak concentrations, or AUCs between subjects with and without ALT elevations. The researchers concluded that the opioids did not appear to contribute to the ALT elevations see among subjects in the active treatment groups as there were no significant differences in the frequency or magnitude of ALT elevation among subjects who took APAP alone and those who took it in combination with an opiate.

Bolesta and Haber (2002)
In 2002, Bolesta and Haber[23] published a literature review that evaluated the potential for APAP to cause toxicity in adult patients without risk factors who used 4 g/day or less chronically. Individuals who took more than 4 g/day APAP, who used APAP for less than four days, or who were less than 18 years of age were excluded. The authors identified four case reports that met these criteria, and these cases are summarized in Table 5.

Table 5: Four cases of acetaminophen-induced hepatotoxicity in adults without risk factors			
Age (yrs)/Gender	**Indication for use/ Medical History**	**Dose/Duration**	**Outcomes**
59 F	Arthritis	2.925 g/day for 1 year	Increased AST Liver enzymes normalized after discontinuation of APAP. Rechallenge resulted in elevated AST.
53 M	Chronic hip and shoulder pain Infectious hepatitis 25 years earlier	3.9 g/day for 13 months	Hepatomegaly, increased AST AST normalized with discontinuation but elevated again with two rechallenges.
25 M	Enrolled in study where subjects received warfarin and APAP	APAP: 1 g QID for 21 days Coumadin; 20 mg on Days 2 and 16.	On Day 18 of APAP, AST and ALT were above normal. APAP was stopped and ALT an AST levels returned to normal baseline levels in two weeks.
67 M	Chest pain, History of heart failure, angina, myocardial infarction One congenital kidney	1 – 3 g/day for 2 – 4 days Other medicines: Furosemide, persantine, captopril, doxycycline.	AST, ALT, total bilirubin, BUN, serum creatinine were elevated on admission. Levels rose for the first few days after admission and then declined. Normal levels after 2.5 months. Serum APAP levels were in the normal range. Patient was treated with N-acetylcysteine.

The authors concluded that patients can develop hepatotoxicity from chronic APAP therapy at recommended doses despite a lack of risk factors for toxicity. They pointed out that such cases may be underreported due to a lack of clinical suspicion of acetaminophen toxicity.

Acetaminophen-Induced Hepatotoxicity in Children

The problem of APAP-related hepatotoxicity is not confined to adults. APAP accumulation in pediatric patients after repeated doses was described over two decades ago by Nahata et al.[24] Although acute liver failure can be a dramatic clinical syndrome, a high index of suspicion is necessary is necessary to diagnose APAP-related hepatotoxicity in very young children. Symptoms are initially nonspecific and may mimic the disorder for which the product was administered, such as a febrile illness in a child with accompanying malaise, anorexia and nausea. Diagnoses can be further complicated in the young child with limited communication ability.

Acetaminophen is the most widely used analgesic and antipyretic in infants and young children worldwide.[25] Pediatric acetaminophen formulations include concentrated drops, liquids, chewable tablets, and meltaways. The recommended maximum daily dose of APAP is 75 mg/kg in children (versus 4 g in adults). Losek et al note that in children from newborn to 11 years, the manufacturer's recommended dose is 7.4 to 14.8 mg/kg/dose, no more than 5 times in 24 hours, which yields 37 to 74 mg/kg/day.[26] Therefore, dosages over 15 mg/kg administered more often than 5 times in 24 hours (>75 mg/kg) result in supra-therapeutic dosing of APAP. Nahata et al estimate the minimum single dose capable of producing liver toxicity at 150 mg/kg in children[23],

while Muniz et al estimate single doses exceeding 200-250 mg/kg may be toxic.[27] The current OTC pediatric dosing for APAP was presented in Table 3. Dosage is based on weight and age.

Reviewer comment:

- *On December 18, 2002, the Division of Over-the-Counter Drug Products (now ONP) completed a Health Hazard Evaluation on a children's APAP product. At that time, there were 17 published cases of severe liver damage reported following multiple dosing of APAP at a total daily dose of ≤ 100 mg/kg. An October 2001 review from the Office of Drug Risk Assessment (now OSE) noted that 11 of 117 children developed severe liver injury after receiving more than 75 mg/kg/day and less than 100 mg/kg/day APAP. Three of these children died.*

FDA Office of Surveillance and Epidemiology Reviews on Acetaminophen Overdose and Hepatotoxicity in Children

Between 2001 and 2002, OSE completed three reviews examining post-marketing reporting data and published literature on acetaminophen overdose and hepatotoxicity in children.

Consult for ONP: Pediatric Adverse Events With Use of APAP (2001)

In 2001, OSE reviewer Carol Holquist completed an internal consult from the Division of Over-the-Counter Drug Products (now the Office of Nonprescription Products) on adverse events associated with use of APAP in the pediatric population. The review included data on APAP from several sources including:

- Sponsor reports to FDA for adverse drug experiences and consumer inquiries for all McNeil *pediatric dosage forms* for the time period 1/1/92-8/31/00

- Sponsor reports to FDA for adverse drug experiences covering misadministration of *adult acetaminophen dosage forms to children* less than 12 years of age for the time period 1/1/92-8/31/00

- Sponsor reports to FDA for reports made to two Poison Control Centers (National Capital Poison Control Center and the Utah Poison Control Center) for *children 0-11 years of age* for the time period 1/1/00-12/31/00.

For all McNeil pediatric dosage forms for the time period 1/1/92-8/31/00, 973 reports were identified using the following COSTART terms: accidental overdose, intentional overdose, and overdose. The search identified 973 relevant reports, and 117 were cases of drug misadministration. Eighty-six of the 117 cases of drug misadministration involved use of various pediatric formulations of acetaminophen while the remaining 31 cases involved unspecified acetaminophen formulations or products. The majority of reports involved use of the 500 mg Extra Strength Tylenol product (65%) mostly by children between 6 and 11 years of age. Table 6 (next page) shows the distribution of these adverse event reports by age and Tylenol product.

Table 6. Post-marketing reports of APAP overdose in children by age and Tylenol product

Age Range	Junior Strength Tylenol (n=3)	Child. Tylenol Chew Tabs (n=17)	Unk APAP Syrup or Elixir (n=3)	Child. Tylenol Susp. or Elixir (n=14)	Infant's Tylenol Concen. Drops (n=50)	Unk APAP Suppository (n=1)	Unk APAP Product (n=9)	Unk Tylenol Product (n=5)	Unk Paracet. Product (n=14)	Panadol (n=1)
0-2 mo.	0	0	0	0	4	0	0	0	0	0
>2-6 mo.	0	0	0	1	8	0	1	0	0	0
>6 mo. – ≤2 yr.	2	1	1	6	32	0	5	2	5	0
>2 yr. - ≤6 yr.	0	11	2	3	2	1	1	1	8	1
>6 yr. - <12 yr.	1	5	0	2	1	0	2	0	1	0
>12 yr.	0	0	0	1	0	0	0	0	0	0
Unknown	0	0	0	1	3	0	0	2	0	0

McNeil submitted a total of 54 case reports involving misadministration of adult APAP dosage forms to children less than 12 years of age. Twelve of these reports were coded as *accidental overdose* or *overdose*, but 35 cases were not coded as overdose but still represented misuse of the adult formulation. One case involved use of an unknown brand of acetaminophen suppository, and six cases involved use of a paracetamol (foreign-marketed APAP) product. Thirty-five reports involved use of Extra Strength Tylenol (65%) and the majority of these involved children six to 11 years of age. Seventeen cases involved some type of hepatic involvement, five of which resulted in death and three in liver transplants. Although the majority of total case reports involved the Extra Strength APAP formulation, the majority of serious injuries occurred in patients who either self-administered or were prescribed an inappropriate dose or utilized an inappropriate dosing interval for the Regular Strength formulation (6). All but one report described multiple dosing of an APAP product. The most common indications for use were fever, URI symptoms, teething, and stomach cramps.

Sponsor-submitted data from two Poison Control Centers (National Capital Poison Control Center and the Utah Poison Control Center) included 1730 cases of APAP exposure in children 0-11 years of age for the year 2000. Of these 1730 cases, 544 (31%) involved APAP maladministration. There were no cases of moderate or major effect or death. Adverse events experienced with APAP combination products appeared to be related to the antihistamine, decongestant, or opioid component of the product. The most common types of errors reported were:

- Incorrect doses secondary to not reading and/or misinterpreting the directions for use of product
- Inadvertent duplicate administrations by parents /caregivers
- Concomitant administration of two acetaminophen-containing formulations
- Administration of the wrong formulation and/or concentration based on the patient's age/weight.

In summary, the majority of calls to the two Poison Control Centers involved single-ingredient APAP pediatric formulations. The specific products most frequently reported in medication error cases were Infant Tylenol Concentrated Drops and Children's Tylenol Suspension or Elixer.

OSE Review of two published case series on APAP-related hepatotoxicity (2002)
In 2002, OSE reviewer, Syed Ahmad reviewed two published case series on APAP-related hepatotoxicity in children and adolescents ages five weeks to 19 years. In 1997, Rivera-Penera et al. reported 73 pediatric cases of APAP-induced hepatotoxicity. The amount of APAP ingested was 77-608 mg/kg/day. Twenty-eight (38%) children had abnormal liver tests at baseline, and of these, six children underwent liver transplantation and one died. The remaining 22 children received conservative management – 21 recovered and one died. Forty-five children with normal liver tests at baseline recovered with conservative management. In 1998, Heubi et al. reported 47 pediatric cases of APAP-induced hepatotoxicity. The amount of APAP ingested was 60 – 420 mg/kg/day, and 24 (52%) of the children received adult APAP formulations. Twenty-four (52%) children died, and three survived with liver transplantation. The reviewer concluded that the following factors contribute to acetaminophen-related liver toxicity in children:

- Miscalculations in dosing by parents and caregivers
- Simultaneous administration of multiple products without the knowledge of parents/caregivers that these products contain APAP
- Administration of adult strength products
- Delayed therapy
- Concomitant ingestion of other hepatotoxic drugs.

Reviewer comments:

- *Rivera-Penera noted that one parent used a teaspoon instead of the dropper for the infant solution (80 mg/0.8 ml), and another used the adult regular-strength tablets (325 mg) instead of the chewable children's tablets (160 mg). They concluded that parental misguidance in dosing children 10 years of age and younger, and "suicide gestures" by children 11 years of age and older, are major causes of acetaminophen overdose.*

- *Rivera-Penera noted that it is unclear whether a viral insult alone or ingestion of therapeutic doses of acetaminophen in the setting of a viral insult together lowers the threshold for hepatic injury.*

OSE Review of AERS data on APAP overdose and associated hepatotoxicity (2002)
In 2002, OSE Safety Evaluator Team Leader Claudia Karwoski identified 307 US cases of liver injury associated with ingestion of one or more APAP-containing products reported to AERS between 1998 and July 2001. Twenty-five cases involved children younger than 12 years of age. None of these cases appeared to involve intentional suicide, but the reporter raised questions about child abuse in two cases. The children ranged in age from less than one day old to 8.5 years. Seventeen (60%) were male, seven were female, and gender for one child was not specified. Twenty-one children were hospitalized; fifteen (60%) had severe life threatening liver injury with liver failure; and ten died.

Twenty-two (88%) cases involved use of only one APAP product. Eleven case reports did not specify the category of APAP product used, but of those that were specified, seventeen cases involved use of a single ingredient APAP product. Use of Infant's Tylenol Drops (100mg/ml) and use of Children's Tylenol Suspension (32 mg/ mL) were reported in seven and five cases respectively. Eleven case reports listed an unspecified APAP or Tylenol product. Potential

contributing factors or confounders were noted in 10 cases (co-suspect medicines or medical conditions).

Eighty-four percent of the pediatric cases involved medication errors. Up to 15 patients received an improper dose due to:

- Use of an improper measuring device
- Misinterpretation of label dosing guidelines or instructions provided by a health care provider (HCP)
- Confusion over differing APAP product concentrations: use of APAP concentrated drops (100 mg/ml) instead of APAP suspension (32 mg/ml).

There were four accidental ingestions of an APAP-containing product and five possible forced ingestions (two cases of possible child abuse and three intrauterine fetal exposures with maternal use of 6-10 g/day APAP). The following list summarizes the circumstances surrounding these 25 cases of APAP hepatotoxicity in children:

- Improper dose (15 cases): Thirteen cases (10 with hepatotoxicity) involved APAP doses higher than the 75 mg/kg/day recommended daily dose

- Wrong formulation (3 cases): In 3 cases, acetaminophen concentrated drops (100 mg/ml) were used instead of acetaminophen suspension (32 mg/ml)

- Accidental ingestion (4 cases): Four cases were classified as accidental ingestion of an acetaminophen-containing product. Three children ingested APAP products while a babysitter was sleeping

- Forced Ingestion (5 cases): Two cases of liver injury were felt to be due to child abuse by the individuals reporting the events. The actual APAP dose could not be determined.

- Medication Error NOS (1 case): An 18-month-old child reportedly following a medication error with an unknown APAP product. The report did not include dose, duration of use, or situational circumstance.

Other Published Data on Acetaminophen-Associated Hepatotoxicity in Children

A PubMed search yielded seven articles published since 2002 that are pertinent to this review, and these sources are summarized below.

Nourjah et al (2006)

As previously described, Nourjah et al published a study presenting national estimates of APAP-associated overdoses obtained by analyzing national database data from 1993 - 2001.[28] The authors used six different surveillance systems that included data from emergency departments (EDs), hospital discharges, mortality data, poison control centers, and spontaneous postmarketing adverse drug event reports reported to the Food and Drug Administration (FDA). Study details and database descriptions are in Appendix B. There were 56,000 emergency room visits and 26,000 hospitalizations for APAP overdose. There were 458 deaths due to APAP

hepatotoxicity, 100 of which were unintentional. Data collected on children younger than 17 years are shown in Table 7.

Table 7: Acetaminophen-associated overdoses in children based on data from national databases (1993 – 2001)

Age	NEISS (ED data)	NHDS (Hosp D/C)	National multiple causes of death file	TESS (poison control)		FDA AERS
				Overall	Fatalities	
< 6 years	17 (±3.29)	2 (±0.49)	< 1 (±0.10)	30 (0.06)	1 (0.07)	NA
6 – 16 years	16 (±3.57)	22 (±1.41)	1 (±0.46)	23* (0.05)	2 (0.15)	4**

*Includes individuals ages 6-19 years
**Reviewed only cases involving individuals 12 years and older

In the NEISS database, about 17% of overdoses occurred in children less than six years of age, and about 16% in children and adolescents ages six to 16 years. Six deaths occurred in children less than 6 years of age.

Squires et al (2006)
Squires et al[29] conducted a prospective, multicenter case study collecting demographic, clinical, laboratory, and short-term outcome data on children from birth to 18 years who presented to one of 24 hospitals in the USA, Canada, or UK from December 1999-December 2004 with acute liver failure (ALF). To participate, subjects met the following inclusion criteria:

- No known evidence of chronic liver disease
- Biochemical evidence of acute liver injury
- Hepatic-based coagulopathy defined as
  - PT ≥ 15 seconds or INR ≥ 1.5 not corrected by vitamin K in the presence of clinical hepatic encephalopathy (HE) or
  - PT ≥ 20 seconds or
  - INR ≥ 2.0 regardless of the presence or absence of clinical HE.

A standard adult clinical coma grade scale was used for older children, and an adapted coma grade scale was used for infants and children younger than 4 years. Diagnostic criteria for acute acetaminophen toxicity included a toxic serum acetaminophen level based on the Rumack nomogram[30] (Rumack-Matthew nomogram) or a history of an acute ingestion of 100 mg/kg within a 24-hour period.

Reviewer Comment
- *In a personal communication Dr. Squires stated that he is not certain whether the cases reflect accidental, intentional, or unintentional APAP overdose.*

Between December 1999 and December 2004, the study enrolled 348 children. The median ingested APAP dose was 183 mg/kg (range 19.2 to 734.1). The authors grouped subjects into three etiologic categories: acetaminophen (APAP), indeterminate, and all other causes. Forty-eight (14%) children had acute APAP toxicity (79% female, 67% white), and two of these children were younger than three years old. Compared to subjects in the two non-APAP etiologic groups, children in the APAP group were statistically more likely to be white and/or female.

Among the 48 children with APAP-associated hepatotoxicity, seven were admitted with coma grade 3 or 4, including both children under age three years. These were the only children who had a moderate to severe peak coma grade. Eight children required ventilator support and five required pressor support. Three children underwent hemofiltration, and three had plasmapheresis. Seven children received red blood cell transfusions and twenty received fresh frozen plasma. Of forty-six children who were successfully followed to study day 21, forty-five survived without liver transplantation, one survived with liver transplantation, and one died following liver transplantation.

The non-APAP causes of ALF in the other 300 children included: metabolic disease (10%), autoimmune liver disease (6%), non-acetaminophen drug-related hepatotoxicity (5%), infections (6%), other diagnosed conditions (10%), and 49% indeterminate. Total bilirubin $\geq$ 5 mg/dl, INR $\geq$ 2.55, and hepatic encephalopathy were risk factors predictive of death or transplantation. However, 20% of subjects with non-APAP ALF and no encephalopathy died or required liver transplantation.

Squires et al. concluded that acute acetaminophen toxicity is the most common identifiable cause of ALF in children $\geq$ 3 years old (21%), but the frequency of ALF due to APAP toxicity is even higher in adults (40%). Instances involving prolonged or inappropriate dosing were not easily captured by this study due to limitations in the study's data reporting form.

Reviewer Comment

- *In a personal communication, Dr. Squires clarified what the authors meant by "Instances involving prolonged or inappropriate dosing were not easily captured by this study". Namely, the data intake form did not have questions that would pinpoint the exact amount, frequency of use and duration of use of acetaminophen.*

Muniz et al (2004)[31]

This is a case report of a 58-day-old girl who presented to a small community emergency department with a two-day history of fever, decreased appetite, lethargy, and irritability. Her medical and birth histories were uncomplicated. The day prior to presentation, she was evaluated by a healthcare professional and had a normal complete blood count and chest radiograph. The parents, as instructed, gave the baby 80 mg (16.3 mg/kg/dose; 98 mg/day) APAP every four hours for fever and reported strict compliance with the recommended regimen.

The baby was admitted to the hospital with severe dehydration and was transferred to a tertiary care pediatric facility and was listless and pale on arrival. White blood cell count and liver transaminases were elevated. Initial AST was 1070 IU/L and ALT was 490 IU/L. Coagulation studies revealed: PT = 37.6 seconds, INR = 3.4, PTT = 42 seconds. Serum APAP level was 287 µg/mL.

Reviewer Comment

- *According to the National Library of Medicine's Medline Plus website,[32] a therapeutic APAP level "depends upon usage." As of December 13, 2006, these reviewers were unable to find references citing an accepted normal therapeutic range for serum APAP*

levels. For a point of reference, see Appendix C, which shows the Rumack – Matthew nomogram and its application in a specific instance of acute APAP overdose: at 8 hours post ingestion, the toxic serum APAP level is about 100 ug/ml and at 24 hours, it is about 10 µg/ml .

The baby was admitted to the pediatric intensive care unit, intubated, and hydrated. She was treated with N-acetylcysteine, blood transfusions, fresh frozen plasma, lactulose, and tube feedings. Liver enzymes peaked on Day 3 and then declined. Serology for viral hepatitis, HIV, cytomegalovirus, and Epstein-Barr virus were negative. Blood and urine cultures were negative. She was discharged home on Day 10 and at two week follow-up had no residual clinical or laboratory abnormalities.

Yeuh-Ping Liu et al (2005)

Yueh-Ping Liu et al[33] described a case of fulminant hepatic failure due to chronic APAP intoxication in a 10-month-old, 6-kg female infant. To treat a respiratory infection, the mother gave the infant 750 mg APAP (125 mg/kg per day) for 4 days plus ketoprofen (50 mg/day) and ibuprofen (60 mg/day). Fifteen hours after the last dose of APAP, the serum level is 55 ug/ml, which is above the Rumack – Matthew nomogram toxic level (see comment below). The child recovered after treatment with N-acetylcysteine. The authors note that the child's clinical presentation needed to be distinguished from Reye's syndrome. They recommend that emergency physicians consider APAP toxicity in any child who received APAP and who shows signs of acute hepatic dysfunction, even if the APAP level is low.

Reviewer Comment

- *While the Rumack-Matthew nomogram for assessing acetaminophen toxic levels is used to assess single dose acetaminophen toxicity, an acetaminophen level below the toxic level line would not necessarily rule out potential acetaminophen toxicity during chronic use. However, if the time from the last dose were known, then an acetaminophen level above the nomogram line during chronic use would reflect a toxic level.*

Shaoul et al (2004)

Shaoul et al evaluated whether silent acetaminophen-induced hepatotoxicity occurs in children with fever. The authors noted children are generally less vulnerable to acetaminophen toxicity than adults. However, there have been reports of hepatotoxicity following therapeutic or mildly supra-therapeutic APAP doses in children with fever, dehydration, and vomiting. The authors conducted this pilot study to:

- Correlate APAP levels with aspartate transaminase (AST) levels, fever, vomiting, and/or decreased calorie intake
- Determine parental knowledge regarding the medication dosage and hazards of APAP.

The study included 107 children who presented to an emergency room in Haifa, Israel. Upon presentation, the children had been treated with APAP with a mean accumulated dose of 197 ± 165 mg/kg over 2.8 ± 1.8 days. The mean serum level of APAP was 4.7 ± 4.7 µg/ml; the highest APAP level was 24.7µg/ml. All APAP levels were in the safety range of the Rumack-Matthew nomogram. The authors did not find any correlation between serum APAP levels and

vomiting decreased food intake and serum AST levels. Subjects with fevers above 39 ^{o}C had statistically higher serum APAP levels than other subjects.

Reviewer comment:

- *As previously noted, chronic APAP use may result in toxicity at serum APAP levels lower than those suggested by the Rumack – Matthew nomogram.*

Sixteen parents administered a single APAP dose above 20 mg/kg, and in more than half of cases, the dose was recommended by a physician. These children had significantly higher APAP levels (though nontoxic) than children who received lower doses. Some parents exceeded the recommended total daily dose of APAP for their children, often following a physician's recommendation:

- 46% administered a daily dose above 60 mg/kg
- 25% exceeded a daily dose of 80 mg/kg (dose recommended by physician: 60% of cases)
- 6% exceeded a daily dose of 120 mg/kg (dose recommended by physician: all cases)

Only 24% of parents were aware of the possible toxicity of APAP. The authors concluded that APAP is relatively safe including acute ingestions of more than twice the recommended dose over a brief period of about 2 days.

Reviewer comment:

- *In the United States, the recommended maximum daily dose of APAP in children is 75 mg/kg. As in some other countries (see Table 9 on page 29 of this review), the recommended maximum daily dose of APAP is Israel may be 60 mg/kg.*

Losek (2004) [34]

This study assessed demographic and clinical characteristics of children receiving APAP per emergency room standing orders (single dose 10-15 mg/kg) and identified factors associated with supra-therapeutic doses (≥ 16 mg/kg). Losek reviewed the records of 661 children cared for during a 1-week period (Feb 1998) in an urban pediatric ED with a 36,000 yearly census. Among these 661 cases, nurses administered APAP to 156 children, 41% younger than two years of age. The indication for APAP treatment was fever in 90% and pain in 10%. Nineteen (12%) of the children received a supra-therapeutic oral APAP dose (17 mg/kg). Two administered rectal doses exceeded 20 mg/kg, while no oral dose exceeded 20 mg/kg. Four of the 19 children had additional risk factors (less than two years old and acutely ill) for acetaminophen-associated hepatotoxicity. The authors noted that a commonly used pediatric reference refers to 20 to 40 mg/kg as the rectal dose for APAP, although the recommended and standing dose per rectum is the same as the oral dose. The authors recommended that emergency departments with standing orders for acetaminophen review their acetaminophen dose accuracy, particularly for the rectal route. This recommendation was reinforced by Bilenko et al. (2006) who noted a similar tendency to administer a supra-therapeutic dose by the rectal route in their cross-sectional survey study of 201 children presenting to the Pediatric Emergency Department of Soroka Medical Center, Beer-Sheva, Israel in 2002.[35]

Comment:

- *Neither Losek et al. nor Bilenko et al. studied children who received supratherapeutic APAP doses for associated hepatotoxicity.*

Lagerløv et al (2003)

In this qualitative study, Lagerløv et al[36] studied Norwegian parents' management of common childhood illnesses including their use of paracetamol (APAP). Parents of pre-school aged children from six Norwegian public health centers were asked open-ended questions about their perceptions of illness, its impact on the family, the use of APAP, and their sources of medical information. The interviews were audiotaped and transcribed. They found that parents judged their child's fever as a cause of discomfort and danger. Parents regarded antipyretics like APAP as a medicine counteracting disease. APAP was used as an important tool for parents in managing different upsets during childhood illnesses. Some parents did not want medical information saying it only added to the burden of the situation or made them anxious. Parents were only slightly concerned about the side effects of APAP. The authors speculated that OTC status may be a reason why APAP safety and efficacy are taken for granted.

American Academy of Pediatrics (AAP) Committee on Drugs: Acetaminophen toxicity in children (2001)[37]

This AAP, Committee on Drugs Policy Statement listed nine recommendations to help ensure safety of acetaminophen in the pediatric population. Recommendations included: continued guidance for parents at well-child visits, a list of drugs that increase the possibility of APAP toxicity, guidance for healthcare providers regarding recognition of acetaminophen toxicity, and parameters for use of N-acetylcysteine. In addition, the Committee provided a list of conditions or situations that may increase the risk of APAP toxicity (Table 8 below):

Table 8: Conditions and Situations That May Increase the Risk of Acetaminophen Toxicity[38,39,40,41]
Diabetes mellitus
Obesity
Chronic under-nutrition
Prolonged fasting
Family history of hepatotoxic reaction
Concomitant viral infection

Concomitant Dosing of Multiple APAP-containing Products and Other Risk Factors

Due to the multiplicity of products on the market containing APAP, there is a risk that more than one of these products will be used concurrently to treat different symptoms. For example, a child with an upper respiratory infection may receive one APAP medicine to relieve fever and another to relieve congestion and cough. As previously summarized by Newgreen, the following situations put children at increased risk of APAP toxicity:

- dose ≥90mg/kg/day
- child is sick (versus a minor ache or pain)

- under two years of age
- treatment exceeds one day
- co-administration of other products that contain acetaminophen
- co-administration of various enzyme inducers (such as phenobarbital)
- incorrect product selection
- off-label uses.[42]

Accurate Dosing of Acetaminophen in Children

Pediatric APAP dosing recommendations vary from country to country. Table 9 shows the dosing regimens in four countries:

Table 9. Acetaminophen dosing regimens in four countries

Country	Single Dose (mg/kg)	Maximum Frequency	Maximum Daily Dose (mg/kg/day)	Duration of Use (days)
Australia	15	Q 4 hrs, up to 4 times/day	60	2
Canada	By age group*	Q 4 hrs, up to 5 times/day	-	5
United Kingdom	10	Q 4-6 hrs	60	3
United States	10-15	Q 4 hrs, up to 5 times/day	75	3 (fever); 5 (pain)

*In Canada, doses are quoted from 0 months to 12 years in a range of 40mg to 480mg, respectively, to maximum daily doses of 200mg and 2,400mg, respectively.

Currently, the dosing chart for pediatric APAP formulations in the United States increases in 80 mg increments. Even with weight-based dosing, the recommended dose for weights at the upper and lower limits of each dose range do not fall within the 10 – 15 mg/kg recommended dose. A citizen petition (77N-0994, CP 14, S45) submitted to FDA through the Public Docket pointed out a potential mismatch between dosing by weight and dosing by age that could result in higher weight children receiving a less than therapeutic dose and lower weight children receiving a supra-therapeutic dose. The petitioner recommended a dosing scheme that used 40 mg increments for children less than two years of age.

The 40 mg increment dosing schedule suggested by the petitioner would change the recommended dose for children 11 months of age from 80 mg to 120 mg. The 80 mg single dose provides 7.1 mg/kg to 10.7 mg/kg APAP per dose for children between the 10^{th} and 90^{th} percentiles for weight by age respectively. The recommended 120 mg dose provides 9.4 mg/kg to 14.3 mg/kg per dose for children between the 10^{th} and 90^{th} percentiles for weight by age respectively. The revised dosing schedule did not include any changes for children over 2 years of age.

The petitioner requested that FDA provide:

- Weight-based dosing for children weighing 12 or more pounds, accompanied by a statement advising that the age-based schedule dosing should be used only if weight is not known
- Age-based dosing for children 6 months of age and older
- Professional labeling for healthcare professionals only with weight-based dosing for children less than six months of age and weighing less than 12 pounds.

FDA is currently drafting a proposed rule that will include 20 mg dosing increments for APAP dosing for children six to 23 months of age. The rule does not change the 80 mg APAP dosing increments for children two to eleven years of age. The label will include a statement that informs caregivers to use weight based dosing unless the child's weight is not known.

Acetaminophen Hepatotoxicity and Acetaminophen Access in the United Kingdom, Ireland, France, and Canada – are there lessons to be learned?

There are published data on the effects of APAP access and pack-size restrictions on APAP-associated hepatotoxicity from the United Kingdom (England, Wales, and Scotland), Ireland, France, and Canada. A number of factors should be considered when interpreting this data and how it should inform decisions regarding APAP access and pack-size restrictions in the United States:

- Some countries primarily address intentional overdose and do not identify or discuss unintentional or accidental overdose, which is a significant issue in the United States
- Outcomes may be influenced by variations in people's cultures and attitudes about medicine use as well as differences in medical systems and related legislation
- Some studies evaluate initiation of new restrictions in a population that has had no previous legislative restriction on access to or packaging of APAP. Other studies evaluate the effects of repealing access restrictions in populations that are accustomed to having access restrictions in place.

Table 11 summarizes APAP access and package restrictions in a number of westernized countries.

Table 11: APAP access in westernized countries[43]

Classification	Countries	Comments
Unrestricted purchase	United States Canada	Until 1999, the following Canadian provinces and territories had place-of-sale restrictions that limited the sale of all APAP strengths > 325 mg and all packages of > 24 tablets of any strength to pharmacies only: Ontario, New Brunswick, Manitoba, Yukon, Nunavut, and Northwest Territories. The package size limit in France is 8 grams (16- 500 mg tablets)
Pharmacy-only in unrestricted quantity Small pack sizes from general retailers	Australia New Zealand UK (prior to 1998)	
Pharmacy-only in limited pack sizes Small pack sizes from general retailers	UK (since 1998) Ireland	
Pharmacy-only in unrestricted quantity	Denmark	
Pharmacy-only with limits on pack size	Belgium Finland France Germany Sweden Switzerland	

United Kingdom (UK)

In the UK, APAP-associated hepatotoxicity has been a recognized problem since the 1970's. APAP-associated hepatotoxicity accounted for 73% of all acute liver failures cases reported from Kings College Hospital during the years 1987 – 1993. Most overdoses in the UK are suicide attempts.[44] A study conducted in the 1970's suggested that patients in the UK did not know that APAP overdose was dangerous. A study conducted by Hawton et al, in 1995, demonstrated that 62 of 80 patients admitted to a hospital for APAP overdose thought that the drug could cause death and 34 knew that APAP could cause liver damage. However, only 18 subjects knew that harmful effects of the APAP overdose would not show for more than 24 hours.[45]

In September 1998, the British government enacted new legislation that made OTC APAP available only in limited quantities (sixteen 500 mg tablets or capsules per pack). Blister packages are used in some cases but are not required. The government's goal was to reduce the number of APAP-related deaths by about 10%. . APAP regulations in the UK require the following:

- 8 g limit (sixteen 500 mg tablets or capsules) for packages of APAP sold in general retail outlets (non-pharmacy stores).
- 16 g limit (thirty-two 500 mg tablets or capsules) for packages of APAP sold on pharmacy shelves with consumer access
- Pharmacists allowed to supply up to 50 g (one hundred 500 mg tablets or capsules) APAP without a prescription at the pharmacists' discretion and in justifiable circumstances. Larger quantities available by prescription
- Labels or consumer information leaflets required to include the following statement: *Immediate advice should be sought in the event of an overdose, even if you (your child) feel well, because of the risk of delayed, serious liver damage.*
- Labels required to include the statement: *Do not take with other paracetamol-containing products.*

Blister or strip packing is not required but many manufacturers use this form of packaging.[46]

Reviewer comments:

- *Based on reports of compliance with this legislation in various regions of the United Kingdom, there appears to be little or no enforcement of the statutes or punishment for retail stores or pharmacies that violate them.*

- *The restrictions do not appear to have limited the number of packages that an individual could purchase at one time.*

Similar restrictions were applied to salicylates where appropriate. Since the APAP restrictions went into effect in the UK, multiple surveys and evaluations of mortality and sales data have tried to define how these changes impacted incidence and severity of APAP overdoses and APAP hepatotoxicity in various regions of the Kingdom. As shown in Table 12 below, the studies overall suggest some positive impact on APAP-associated morbidity and mortality.

Overall, data from the UK suggest that APAP package size and access restrictions resulted in decreases in APAP-associated deaths, admissions to liver units, presentations to hospitals for overdose, and number of APAP tablets ingested, at least in the initial two years following legislation. There are regional variations and most of these overdoses are considered intentional. There is no data addressing unintentional overdose. In their 2004 review of the effects of restricting paracetamol in the UK, Morgan and Majeed noted that only three studies distinguished between poisonings due to APAP alone and those due to APAP combination drug products. They noted that two thirds of APAP-related deaths and 10% of hospital presentations in the UK involve APAP combination products, like Co-proxamol (APAP + dextropropoxyphene), which are not sold OTC and that this might dilute the observed effects of the legislation.[47] Morgan and Majeed and other commentators criticized the short follow-up time after legislation in many of studies. One of the legislations intents was to reduce household APAP stocks, which may require longer periods of time than those studied. In Scotland, the APAP-associated mortality rates are twice that in England and Wales, and while study data are more limited, they suggest that the legislation did not significantly reduce APAP poisonings or deaths beyond one year post-legislation.

Reviewer comment:

- *In a personal communication, Dr. William Bernal, hepatologist at King's College, England, stated that there is little doubt that both the numbers of patients developing serious (APAP-associated) hepatotoxicity and those with more trivial (APAP) poisoning have significantly decreased since the introduction of sales restrictions and labeling changes (in the United Kingdom). If given the choice, he would without hesitation, again support APAP restrictions and believes that the majority of the hepatology community in the U.K. would as well.*

Table 12: Summary of Studies Evaluating Effects of APAP Package Size and Distribution Limitations on APAP Overdose and Hepatotoxicity in the United Kingdom

Study	Study Period	Location	Data Sources	Findings
Prince et al (2000)	10/1995 to 09/1998 compared to 09/1998 to 12/1999	Northern England	Reviewed records of patients admitted to a liver unit and patients listed for liver transplantation	▪ Monthly number of referrals to the transplant list fell from 3.5 to 2 ($p<0.02$) ▪ Median number of monthly referrals to the liver unit fell from 2.5 to 1 ($p<0.02$) ▪ 25% of referrals were alcoholic or on anticonvulsants Overdose severity remained unchanged.
Turvill et al (2000)	09/1995 to 08/1999	London	Reviewed all records of patients admitted to the Royal Free Hospital with APAP overdose	▪ 21% reduction in APAP overdose cases ▪ 64% reduction in patients requiring treatment with N-acetylcysteine ▪ Savings of 200 inpatient hospital days No change in proportion of overdoses with benzodiazepines.
Robinson et al (2000)	01/1998 to 06/1998 compared to 01/1999 to 06/1999	Northern Ireland	Reviewed all APAP poisoning admissions to five general hospitals in Belfast (N = 594)	▪ Serum APAP concentration at 4-6 hours post-ingestion decreased from 37 to 27 mg/L ($p = 0.003$) Number of patients admitted with APAP poisoning did not change significantly but trended down (398 to 374).
Thomas and Jowett (2000)	02/1998 to 08/1998 compared to 02/1999 to 08/1999	Wales	Reviewed records of 116 overdose patients admitted 6 months before and 112 overdose patients admitted 6 months after APAP legislation.	▪ Number of APAP overdoses decreased from 52 (45%) to 40 (36%) ▪ Number of overdose patients who took more than 16 tablets: 30 (68%) before and 18 (51%) after the legislation ▪ Number of non-APAP overdoses increased from 64 to 72 (often with drug mixtures including tricyclic antidepressants Number of hospital days unchanged
Sheen et al (2002)	1998, 1999, 2000	UK and Northern Ireland	Intercontinental Medical Statistics Services data	The UK OTC supply of APAP declined from 409 million grams (1998) to 166 million grams (2000). Ibuprofen supply up by 74% (26.4 million grams to 46 million grams)
Hughes et al (2003)	04/1995 to 09/1998 compared to 09/1998 to 01/2003	England	Reviewed admissions to Queen Elizabeth Hospital liver unit and the number of patients admitted to the University Hospitals in Birmingham with APAP overdose	▪ Prior to legislation, the average number of admissions per year for APAP overdose was 360. After legislation, admissions decreased to 250/year (31% reduction). ▪ Admissions to the liver unit declined from 76/year before legislation to 38/year after legislation (50% reduction).
Inglis JH (2004)	1990 to 1991 compared to 2001 to 2002	Scotland	General Registrar Office annual reports: deaths and emergency admission data	▪ After the 1998 legislation, APAP-associated deaths fell 45% in the first year but rose in the 3 subsequent years to reach pre-restriction levels. ▪ With the restrictions, APAP poisonings fell by 14% the first year and stayed lower the second year but increased 10% in each of years three and four to new record highs.

continued

Table 12: Summary of Studies Evaluating Effects of APAP Package Size and Distribution Limitations on APAP Overdose and Hepatotoxicity in the United Kingdom

Study	Study Period	Location	Data Sources	Findings
Hawton et al (2001, 2004)	1993 to 9/1998 compared to 9/1998 to 2003	England Wales Scotland	▪ Data on drug related deaths from the Office for National Statistics (1993 – 2001) ▪ Liver transplants and referrals to all liver units except one in England and Scotland (1996 – 2002) ▪ APAP self-poisoning presentations to five general hospitals (1997 – 2001) ▪ Statistics on sales of analgesics to pharmacies in the UK before and after 1998 legislation	▪ The three years after legislation showed sustained decreases in deaths due to single ingredient APAP (-29%) or salicylate (-46%) products. Similar decreases occurred with combination products. ▪ On the basis of mortality data from 1993 to 1998, 118 deaths involving APAP and 81 deaths involving salicylates were avoided. ▪ Deaths involving ibuprofen were few: 11 deaths in the five years before legislation and 13 deaths in three years after legislation. These deaths also involved other drugs. ▪ There was a 30% reduction in admissions to liver units for APAP induced hepatotoxicity. Mean annual admissions for APAP poisoning decreased from 349/yr from 1996 – 1998 to 230/yr from 1998 to 2002. ▪ During the first year after legislation, hospital presentations for APAP overdose decreased by 9 – 21% but no further decreases occurred thereafter. The number of ibuprofen overdoses increased by 11 – 44% in the second and third years after legislation. ▪ The number of tablets ingested in APAP and salicylate overdoses decreased significantly during the 3 years after legislation. ▪ The total numbers of APAP tablets sold was similar before and after legislation. Pack size went down and number of packs sold went up.
Bateman et al (2006)	1995 to 1998 (Q1) compared to 1998 (Q2) to 2000 (Q2) compared to 2000(Q3) to 2004	Scotland	▪ General Register Office for Scotland: for overall deaths by APAP poisoning with and without alcohol or co-ingested medicines, overall, APAP + propoxyphene, and APAP + codeine ▪ APAP overdoses from acute hospital discharge database ▪ Prescription data for APAP compounds	▪ Focused on in-hospital deaths which they felt more likely due to APAP effect. Most out-of-hospital deaths involved other drugs whereas the majority of in-hospital deaths involved APAP use with or without alcohol. Overall most deaths involved co-proxamol (APAP + propoxyphene). ▪ The number of APAP-related overdoses decreased among children under age 10 years and among youths ages 10 to 19 years. However, overdoses increased among adults and the elderly. ▪ The authors noted that poisonings overall were increasing in Scotland in the 1990's and then declined. This makes it more difficult to interpret legislation effects; however, it appears that the legislation has been unsuccessful in Scotland.

Other countries
In France, APAP is a commonly used analgesic but the content of each pack of APAP has been legally limited to 8 grams since the 1980's. Liver failure due to APAP has always been much less common in France than in the UK. France has fewer than 10 cases of APAP-induced liver failure per year (as of the year 2000).[48]

In 1997, the Republic of Ireland introduced tighter APAP packaging restrictions than the UK. These restrictions were recommendations until 2001 when they became law. Emergency supplies of 12 tablets are available for general retail sale, and packets of 24 tablets can be purchased at the pharmacy. These limits parallel restrictions in Finland that were introduced in 1976. In 2000, Donohoe and Tracey examined 2020 cases (1044 in 1997 and 976 in 1998) of acute intentional APAP poisoning. More than 50% of cases involve ingestion of 24 or fewer tablets with no significant difference between the two study years. There was a statistically non-significant decrease in the number of poisonings with 48 or more ingested tablets. The authors concluded that the voluntary reduction in pack size did not result in a decrease in APAP overdose. However, the study did not evaluate any change following legislation reducing pack size. It is important to note that APAP was blister packaged in Ireland even before the 1997 recommendations and the 2001 legislation that reduced pack size.

Data from Canada suggest that provinces with long standing restrictions on package size have lower annual rates of hospitalization for APAP overdose than provinces where APAP distribution was unrestricted for more than 30 years. In 1999, remaining provincial restrictions on the sale of APAP were lifted. Comparing the 1.5 year periods preceding and following the statutory change, there were no changes in the annual incidence rates for acetaminophen overdose hospitalizations. The study was conducted by McNeil Consumer and Specialty Pharmaceuticals, and the authors did not comment on the lower rates of hospitalizations for APAP overdose in provinces and territories with package size restrictions. **It is possible that individuals who grow up with APAP in small packages and with restricted access develop different beliefs and attitudes about APAP that lead to different use behaviors.**

Comment:

- *The introduction of new APAP access and package restrictions to a population of consumers, who have had unrestricted access, is different from removing APAP restrictions in an area where consumers have been accustomed to restrictions for many years. Legislation changes that alter consumer access to APAP will probably lead to different effects on consumer APAP use behaviors based on consumers' baseline attitudes and beliefs about the safety and efficacy of APAP as a medicine and as a mechanism for suicide. Individuals who have grown up with restricted access to APAP may view the drug differently than individuals who have grown up without such restrictions.*

When extrapolating these data from the United Kingdom and other countries to the United States population, a number of differences should be considered. Cases of acetaminophen overdose in the United Kingdom are nearly exclusively associated with intentional overdose. In the United States, it appears that about 10-15% of acetaminophen overdoses and about 25-30% of acetaminophen-associated hepatotoxicity cases involve unintentional overdose. This difference

may, in part, be due to a different threshold for nonessential use of medicines. The positive impacts of blister packaging and package size restrictions may differ in size and character for American consumers with intentional APAP overdose and American consumers with unintentional APAP overdose. For example:

- If an individual uses an APAP product and does not achieve adequate pain or fever relief, the individual may take more drug, take a different drug, or contact a healthcare professional for advice. With blister packaging that includes prominent warnings and directions for use, a person is more likely to recognize how much drug they have consumed over a given period of time (e.g. over a day) and the repercussions of overdose. Perhaps this will increase the likelihood of seeking advice from a healthcare professional before unintentional APAP overdose occurs.

- An individual who impulsively chooses to make a suicidal gesture with APAP overdose may have time to reconsider their actions if they have to pop each individual tablet or capsule out of a blister pack and read a liver toxicity warning while doing it.

- Regardless of package size limitations and package configuration, an individual who is truly suicidal and plans out a suicide by APAP overdose may take all actions necessary to have a fatal dose of APAP available. However, data from the United Kingdom suggests that the size of the overdose may decrease when package sizes are smaller and blister packaging is used. In addition, empty blister packages sometimes allow family to accurately report the amount of drug consumed to hospital personnel caring for an individual with APAP overdose in the emergency room.

Minimizing Acetaminophen-Associated Hepatotoxicity: Exploring Intervention Options

The next portion of this paper presents potential regulatory actions followed by potential educational outreach approaches for both healthcare professionals and consumers. This list, while comprehensive, may not include all possible ways to effect change.

1. Limit OTC package size

Data from the U.K. suggests that package size restriction may reduce the occurrence of intentional and unintentional APAP overdose. These restrictions were put in place primarily to reduce the occurrence of intentional overdose. In the United States, unlike in the U.K., intentional APAP overdose is not one of the primary methods for committing suicide. So, it is not clear whether package restrictions in the United States would have the same impact as in the U.K. or whether the effect on APAP hepatotoxicity would be more or less robust.

OTC acetaminophen package sizes could be limited to 36-count packages for 325 mg solid dosage forms and 24-count packages for all 500 mg solid dosage forms, as was done in the U. K. This package size would provide enough acetaminophen for maximum dosing for three days for an adult. This is the current labeled duration of treatment for fever. The current duration of treatment for pain in adults is ten days. However, after three days of pain treatment, a consumer

would need to decide whether to start a new package of APAP or to speak with a healthcare professional.

Pros:

- Evidence from the U.K. experience suggests that limiting package size may reduce the number of pills ingested on impulse due either to frustration with unrelieved pain or suicide gesture/intent.
- In addition, despite some noncompliance in the general sales stores and pharmacies with package number sales restrictions, there has still been a reduction in overdoses.
- More obvious when a lot of drug is being used over time – may make a consumer more likely to recognize that adequate pain relief is not being achieved with correct use and that a healthcare professional should be consulted
- If an individual needs APAP to treat their fever or pain for more than three days, they need to actively decide whether to start a new pack of medicine. It is possible that this active process of finishing one pack of medicine and starting another may lead some consumers to consider whether to consult a healthcare professional before continuing self-treatment.
- The monograph already has package size restrictions on some products (e.g. sodium phosphate, flavored aspirin for children, fluoride toothpaste).

Cons:

- In the past the Office of Chief Counsel has raised questions about whether we have the legal authority to limit package size (e.g. ephedrine). Industry may argue that we do not have the authority.
- It is not clear that data from the U.K. predict what would occur in the United States. The U.K. restrictions were intended to reduce intentional overdoses. It is not clear how package size restrictions would impact *unintentional* APAP overdoses.
- Family members will need to purchase packages of acetaminophen more often (but probably not more often than they need to go to the grocery store or pharmacy for other items).
- The products will likely cost more to purchase in smaller packages.
- Many people who use acetaminophen correctly may be upset by package size restrictions and increased product cost.
- Individuals, who use APAP regularly to control the symptoms of osteoarthritis and degenerative joint disease, would need a cost effective mechanism to purchase larger quantities.
- It is not clear whether package size restrictions alone would limit the number of APAP packages that an individual could purchase at one time. The value of restricting the *number* of packages at purchase would need consideration.
- If the United States decided to restrict APAP package size and the number of packages that could be sold at point of sale, then legislation would need to include consequences for noncompliance and consideration of enforcement measures.
- Pharmaceutical companies and retailers will not readily agree with this.

2. Require blister packaging for OTC with enhanced labeled warnings on the blister packs.

Research on consumer warnings suggests that a product warning is more effective when users must physically interact with it during product use. [49] This means that the warning is placed where it temporarily interferes with task accomplishment and thus increases the likelihood that the warning will be processed in a meaningful way. Such warning placement interrupts a person's *script* or routine and demands attention. In a comparative study, versions of warnings placed where they interrupted the users interaction with the product produced 46% compliance compared to 10% compliance for warning placements that did not interfere with task accomplishment. Studies with medications and non-medication products show that placement of the warning on the product itself (rather than the outer carton) increases the likelihood of a user noticing the warning.[53]

Packaging acetaminophen-containing products in cardboard wrapped blister packs could offer this physical interaction at the time of drug use. Key safety messages and directions for use could be repeated in larger font size on the cardboard face adjacent to the blisters, forcing the consumer to see this information each time the product is used. For example, this packaging method could work with a multi-day treatment card where the card contains 8 to 12 grams APAP (16 to 24 tablets of APAP 500 mg) or with daily blister pack cards that come in a box containing 7 or 14 daily cards.

Changes in package configuration should be considered for OTC APAP-containing drugs. For solid dosage forms, tablets and capsules should be packaged in labeled blister packs that contain additional visual reinforcements of warnings and directions for use. Pop-out blister packs encased in a card would allow portability of the product with all of its drug information. It would also provide a mechanism for keeping track of how much drug was taken that day. The number of missing units from a blister pack is a visual signal to a consumer whereas, it is not possible to tell whether there are two fewer tablets in a bottle of 100 tablets.

Pros:

- Consumer can see how many pills have been used. A blister pack or card provides a visual reminder of how many tablets or capsules have already been used. This may reduce unintentional double dosing.
- Makes impulsive chugging of more than two pills less convenient
- Allows additional surface area on packaging to reinforce key warnings and correct dosing information if the blister pack is enveloped in a cardboard casing.
- There are some published data on the use of blister packs or blister calendar packs to improve compliance with single or multi-drug regimens for prevention of graft rejection and treatment of malaria, tuberculosis, leprosy and sexually transmitted infections.[50,51,52]

Cons:

- Harder for older individuals with arthritis to get the pills out, but these individuals could obtain prescriptions for the drug.
- Packaging may be more expensive which could translate into greater drug cost to the consumer.

- Does not address use with liquid formulations.
- This is likely to raise legal issue(s) with the Office of Chief Counsel.

3. Consider removal of acetaminophen from some or all OTC combination drugs

Surveys conducted among consumers and information gathered from patients with acetaminophen-associated hepatotoxicity suggest that many consumers are not aware that acetaminophen is in some of the OTC and prescription products that they use. This results in unintentional overdose when more than one drug product is used concurrently. A similar and more common problem occurs with concurrent use of a prescription pain reliever and an OTC pain reliever or combination drug product with acetaminophen. Labels for prescription drugs are regulated by State Boards of Pharmacy. They are not standardized and do not always clearly inform patients/consumers about the drug's active ingredients.

Reviewer comment:

- *This regulatory change could be considered for ibuprofen and naproxen products as well as acetaminophen products to encourage consistent medicine decision-making across the class of pain reliever/fever reducer products. The purpose of this regulatory change is to minimize the unnecessary and unrecognized use of all OTC analgesic/fever reducer active ingredients.*

Pros:

- May decrease the likelihood of a consumer using two OTC APAP-containing products concomitantly, such as a combination product to treat congestion and cough and another product for headache

Cons:

- Convenience factor of combinations is eliminated.
- Forces consumers to buy their fever reducer/pain reliever separately and take two medicines rather than one when they have a combination of symptoms that happen to include fever or headache.
- Industry is likely to actively resist this because it will eliminate many products from the market.
- It is not clear what data we could use to support this other than it makes sense that fewer products would likely lead to fewer episodes of concomitant use of more than one OTC APAP-containing product.
- This is likely to raise legal issue(s) with the Office of Chief Counsel.

4. Modify and expand label warnings included in the Proposed Rule for internal analgesics warnings

Currently, OTC acetaminophen-containing products are not required to carry an organ specific warning except for that associated with the alcohol warning:

If you consumer 3 or more alcoholic drinks every day, ask your doctor whether you should take acetaminophen or other pain relievers/fever reducers. Acetaminophen may cause liver damage.

In December 2006, FDA published a Proposed Rule that included (among other warnings) the following liver warnings for adult acetaminophen products and pediatric acetaminophen products (71 FR 77314 @ pg 77349-50):

Adult formulations:

Liver warning: This product contains acetaminophen. Severe liver damage may occur if you take

- *more than (max # daily dosage units) in 24 hours*
- *with other drugs containing acetaminophen*
- *3 or more alcoholic drinks every day while using this product*

Pediatric formulations:

Liver warning: This product contains acetaminophen. Severe liver damage may occur if the child takes

- *more than 5 doses in 24 hours*
- *with other drugs containing acetaminophen*

The warnings in the Proposed Rule provide the needed liver specific warning for acetaminophen-containing products. It makes sense to combine the alcohol warning with the liver warning since chronic alcohol use is one factor that may contribute to APAP-related hepatotoxicity. However, small changes in the wording of the warnings and incorporation of information related to gender differences may help to optimize accuracy, comprehension, and impact. Women develop adverse health consequences from the use and abuse of alcohol over shorter time periods and with lower consumption than men.[53] On average, women are smaller and tend to have a higher percentage of body fat and a lower percentage of body water than men. Therefore, if a man and a woman of the same weight ingest the same amount of alcohol, the woman will tend to achieve a higher blood alcohol concentration.[54] As a result, we may need to consider incorporating weight and gender-related differences for alcohol consumption into the liver warning language on adult APAP formulations.

In addition, published data and additional data presented at the NIH Acute Liver Failure Workshop (December 4, 2006) suggest value in requiring the following two warnings on the *Drug Facts* label for all APAP-containing drug products:

Ask a doctor before use if you

- use prescription pain medicines
- have hepatitis or other liver disease. You may need a different dose.

Reviewer comment

The Proposed Rule has the following wording: "Do not use with any other drug containing acetaminophen (prescription or nonprescription). Ask a doctor or pharmacist before using with other drugs if you are not sure" and "Ask a doctor before use if you have liver disease."

While not all people heed label warnings, there are some data suggesting that label warnings will be read by consumers. A 2004 study by Nabors et al assessed label reading in 876 high school and college students. Most reported reading labels or package inserts to learn about medicines. Participants experiencing pain (except headaches) were more likely to read the labels. Participants were interested in information about side effects, ingredients, dosage instructions, and symptoms related to use.[55]

Pros:

- Research on consumer warnings suggests that providing more explicit or detailed information in a warning message increases the warning's effectiveness.[56]
- The more explicit warnings may encourage patients/consumers to initiate a dialogue with their healthcare professional about concomitant use of multiple drug products for treatment of pain, thereby avoiding unintentional acute or chronic APAP overdose.
- Data presented by Julie Polson, M.D. at the NIH Acute Liver Failure workshop suggest that individuals with hepatitis may have a lower threshold for APAP-associated hepatotoxicity with use of recommended doses of APAP.[19]

Cons:

- More information to read on the label, which could theoretically detract from comprehension of other label elements.
- Some people don't read the labels now, so it is not clear that they will read new warnings.

5. Acetaminophen identification: principal display panel (PDP) requirements

The Proposed Rule for acetaminophen warnings includes a requirement that the name *acetaminophen* appear on the principal display panel, as part of the established name, for all OTC drug products containing acetaminophen. The Proposed Rule includes the following requirements for size and appearance of the word *acetaminophen* on the PDP:

> *Manufacturers determine the prominence of the name "acetaminophen" on the PDP by selecting from the two options listed below, the print size option that is greater:*
> - *the name "acetaminophen" is at least one-quarter as large as the size of the most prominent printed matter on the PDP or*
> - *the name "acetaminophen" is at least as large as the size of the "Drug Facts" title, as required in 21 CFR 201.66 (d)(2).*
>
> *The name will be highlighted (e.g. in fluorescent or color contrast) or in bold type so that the name is prominent and stands out from other text.*

In addition, FDA should consider standardizing the appearance of these words on the PDP in terms of font and color contrast to maximize rapid consumer recognition. Because packages are many different colors, it may be necessary to come up with a design that ensures prominent appearance on all color backgrounds. Consumer warning research suggests that color is one of

the most important features that can help a warning stand out, and the effectiveness of the color depends on sufficient contrast from its surroundings. The three color combinations that provide the greatest contrasts are: black on white; black on saturated yellow; and white on saturated red. Other data support the use of mixed case type in a simple font without serifs (like Arial) except where the print is very small. This information should be used to define a limited number of options for the color and appearance of the active ingredient name on the PDP's for acetaminophen, NSAID, and aspirin containing products.[57]

Pros:

- Establish rapid consumer recognition of APAP as an active ingredient in APAP-containing products.
- More obvious to consumer when two drug products both contain APAP. This may decrease incidences of unintentional overdose through concomitant use of two APAP - containing products.

Cons:

- For this change to have impact the consumer needs to understand that taking too much APAP can be harmful. Also, the consumer needs to read and adhere to the label warning that states: *Do Not Use with other products containing acetaminophen*.

6. Restrict the number of different dosage strengths by standardizing acetaminophen concentration for all liquid dosage forms and for pediatric solid dosage forms.

Currently, there are two concentrations for liquid/suspension formulations of acetaminophen: 80 mg/5 mL (suspension) and 80 mg/0.8 mL (concentrated drops). Published studies suggest that parents confuse dosing across these two different pediatric product concentrations and that many parents mistakenly believe that the infant drops (80 mg/0.8 mL) are less concentrated than the children's suspension.[58,59] Some investigators have argued that all non-solid acetaminophen dosage forms for adults and children should contain 80 mg/0.8 mL and that these dosage forms should include a measuring syringe marked with all of the weight-based doses included on the label.[60,61] Products labeled for adults could provide a syringe or a cup that successfully delivers the correct dose.[62] While data suggest that the acetaminophen concentrated infant drops are associated with more dosing errors than the children's suspension, it is not clear that this would be the case if the suspension concentration was not available. The use of the higher concentration would allow easier dosing in small (and possibly all) children and would allow the use of the same drug concentration and dosing calculations for all consumers from infancy to adulthood.

Sponsors could be restricted to marketing the fewest number of pediatric solid doses needed to accommodate the labeled dosing range from ages 2 to 11 years. Marketing of more than one pediatric solid dose formulation, where one formulation might conveniently cover the full pediatric dosing range, may cause consumer confusion. This is especially true if the packages and pills look very similar. For example, McNeil Consumer Health manufactures two dosages of Tylenol Meltaways – an 80 mg tablet and a 160 mg tablet. Both tablets are pink or purple and chewable. Both packages look nearly identical except that one is called *Jr. Tylenol Meltaways*

(160 mg) and one is called *Children's Tylenol Meltaways (80 mg)*. The *Jr. Tylenol Meltaways* is labeled for children ages 6 years and older. The *Children's Tylenol Meltaways* label includes dosing for children ages 2 to 11 years of age with the lowest recommended dose being 2 tablets. Confusion may occur when dosing children, especially if both products are available in the home and more than one child is being dosed.

If a situation arises where two different tablet strengths are needed to accommodate convenient and correct dosing for all ages, then the packaging of the product should clearly distinguish the two strengths using differences in name, color, and explicit communication about tablet strength and ages for use.

Reviewer Comment:

- *This process can be easily monitored and overseen with NDA products. Defining this process for Monograph products would be challenging but worthwhile in order to ensure ongoing availability of chewable dosage forms for children.*

- *This concept could be applied to ibuprofen and naproxen products as well.*

Pros:

- One dosing scheme and one drug concentration for acetaminophen liquid dosage forms may reduce medication errors/overdose caused by use of multiple products with different dosing schemes. This may benefit use in children and in adults.
- Minimizing the number of pediatric solid formulation strengths may decrease medication errors especially if different strengths are visually demarcated by differences in color, and perhaps size, with clear labeling that emphasizes differences.

Cons:

- If the infant concentrated drops are available, but not the suspension (liquid), then the product with the most dosing errors is retained (see discussion below). If the children's suspension (liquid) is available, but not the concentrated drops, then it may be difficult to get infants to swallow an adequate dose.
- If the suspension is removed from the market and healthcare professionals are not well informed of this change, an increase in pediatric APAP overdose and APAP-associated hepatotoxicity could occur. Physicians could erroneously instruct parents to treat their children based on the dosing recommendations for the less concentrated suspension.
- It is not clear whether there is sufficient data to support this restriction. Most known cases of APAP toxicity following an overdose with an inappropriate or incorrect dosage strength are case reports.

7. Change dosing so that single maximum dose is up to 650 mg and/or maximum daily acetaminophen dose is less than 4000 mg per day.

Revision of the single dose and/or maximum daily OTC acetaminophen dose could be approached in one of two ways:

Remove the 500 mg unit dose from the OTC market (could be available Rx). Leave the 325 mg unit dosing the same

Pros:

- Makes the 500 mg tablet less accessible, and encourages consumers to use the lowest effective acetaminophen dose for the treatment of pain and fever.
- People who may be more sensitive to the toxic effects of APAP (it is not clear who they all are) will use a lower dose if they follow label instructions.

Cons:

- Efficacy and safety data suggest that 1000 mg of acetaminophen offers greater efficacy than 650 mg acetaminophen for the short-term treatment of acute pain (two studies on post-delivery episiotomy pain) with a similar safety profile.[74]
- Dose ranging data for fever reduction may not be available.
- Lower efficacy with the 650 mg dose could lead to more frequent dosing without lowering total daily dose or could lead to concurrent use with other OTC pain reliever/fever reducer drugs.
- If consumers fail to achieve adequate pain relief, they may take more medicine than instructed on the label despite any label warnings about the risks of hepatotoxicity.
- Industry is unlikely to support this change.
- Most people are not at risk for liver toxicity with the 4000 mg /day total dose.

Leave 500 mg and 325 mg units in the monograph but change the total daily dose to 3.0 to 3.25 g: For 500 mg Extra-Strength formulations: take 1-2 tablets every 6 hours up to 3 doses per day. For 325 mg Regular Strength formulations: take 2 tablets every 4 hours up to 5 doses per day.

Reducing the total daily dose of acetaminophen to 3.25 g/day may be the more reasonable of the two options; however, both options may add to, rather than reduce, the unintentional overdose problem. Acetaminophen is effective at relieving mild to moderate pain for some people. The 1000 mg dose is more effective. Failure to obtain pain relief with lower doses may encourage greater deviation from recommended dosing due to poorer pain control. Strong label warnings, package size limits, and package configuration changes combined with strong, clear educational messages may be more likely to change consumer behaviors in ways that improve drug use safety than regulatory measures that decrease the efficacy of the drug.

Pros:

- The 500 mg dose of APAP remains available. This is the most commonly sold dose unit of APAP. There are data that support that a 1000 mg dose of APAP is more effective than 650 mg APAP for relief of pain.
- The lower maximum daily dose is less likely to cause hepatotoxicity in more susceptible individuals.

Cons:

- Changing the directions for use on the label of the 500 mg dose unit bottles may not change overuse behaviors driven by persistent pain. The label directions are already being ignored.
- The duration of effect for acetaminophen may leave some consumers with a six hour period of time where they do not have adequate pain or fever control.
- It is rare for an individual to develop acetaminophen-associated hepatotoxicity using 4 grams per day of acetaminophen. While this may occur more often in chronic users and abusers of alcohol and individuals with anorexia with or without viral illness, label warnings could address these groups. Other populations with increased risk can not be readily identified at this time.

8. Package Insert for all OTC acetaminophen-containing medicines

A package insert (PI) could reinforce warnings on the Drug Facts label. The PI could caution consumers against concomitant use of different APAP-containing products to treat different symptoms. The insert could also inform consumers that some prescription pain products contain APAP and should not be used concomitantly with OTC APAP-containing products.

Pros:

- Reiterates information on warnings and correct use of APAP-containing products to consumers.

Cons:

- Consumers may not read the PI. This may not be an effective means through which to communicate risk. Unless the materials are read and lead to retained information, any benefit will remain unrealized.

9. Educational initiatives for healthcare professionals

- **FDA science paper with complementary healthcare provider information sheet and patient information sheet through the Drug Safety Board**
  This information could be announced with a press release. The professional trade press often picks up this information and draws attention to it.

- **Articles and/or letters to the editor in professional journals about issues with unintentional overuse of acetaminophen-containing products and hepatotoxicity**
  This initiative should begin when regulatory changes become public. Articles from FDA should summarize the acetaminophen toxicity issue in the United States and then focus on the regulatory and educational actions being taken and methods for follow-up of effects of these changes over time.

- **CME module on Safe Pain Management**
  Teach providers to inform their patients about the active ingredients in their prescription pain relievers and how they correspond with OTC analgesics. Healthcare providers need to provide explicit information to patients about prescription medicines that can and can not be

used with various OTC analgesics. Encourage professional associations and other organizations that offer online CME to offer the module on their websites.

- **Dear Healthcare Professional Letter**
  Present and explain package and labeling changes for OTC drug products containing APAP.

Pros:

- These initiatives could broaden awareness of combination products containing APAP.
- These initiatives could heighten awareness of unintentional overdosing through concomitant use of multiple acetaminophen-containing products.
- These initiatives could encourage prescribers to inform their patients when their prescription analgesic contains acetaminophen and to warn them against using their analgesic with OTC products containing acetaminophen.

Cons:

- Considerable Agency time and monetary resources may be needed to prepare and disseminate educational materials for these initiatives.

10. Educational initiatives for consumers

The consumer educational campaign should occur in two phases. Phase I would precede any proposed regulatory changes and could enter planning and development immediately. Phase II would begin with publication of any and all regulatory changes and continue. In addition, FDA could partner with other government agencies, such as the CDC, to advise and educate consumers about drug-induced liver toxicity. While some consumer education about APAP has been done it is clear that more is needed.

Phase I: Pre-Regulatory

OTC Medicines are Serious Medicines: Getting to Know Your Medicines for Pain and Fever

- **Goals:**
  - Change consumer belief that OTC medicines are innocuous. Teach that OTC medicines are serious medicines and can be harmful if used incorrectly.
  - Build consumer awareness of safe use of OTC medicines, especially analgesics. Teach use of the Drug Facts label and simple do's and don't about using medicines.
  - Introduce consumers to the organ specific risks associated with analgesic use and overuse. Focus on knowing active ingredients in both OTC and prescription medicines.

- **Educational Messages**
  Would include the following:
  - Read the label. Know your active ingredients and what they do.
  - Do not take two medicines that contain the same active ingredient at the same time (not in the same dosing window)
  - Do not take more than recommended. If the medicine does not work, do not take more. Call your doctor or pharmacist.

- Do not take for longer than directed. You may have a more serious problem. Call your healthcare provider.
- Measure your liquid medicine with a medicine measuring tool
- Keep track of when you use your medicine and how much you use
- More is not better. If the recommended dose of medicine does not work for you, it may not be the right medicine for your problem. Call your doctor or pharmacist for advice.
- Tell your healthcare providers about ALL the medicines you use….the over-the-counter ones too.
- Discuss how some people may be more at risk for liver toxicity due to underlying liver disease or alcohol intake.

- **Routes of Dissemination**
  Could include the following:
  - Press Release
  - PSA's (consider resurrecting the black PSA from the 2004 campaign with modifications based on focus group feedback)
  - Medicines in My Home website lesson on "Pain and Fever Medicines" (target audiences: adult, parents, secondary school teachers and students)
  - FDA and You article on "Pain and Fever Medicines" (target audience: secondary school teachers and students)
  - Partner with NIH to create educational materials: web and print

Phase II: With and Post-Regulatory Changes
A "Have You Noticed?" Campaign

- **Goals:**
  - Encourage consumers to link changes in the appearance, size, and configuration of their analgesic-containing OTC medicines to the importance of using these medicines correctly and the dangers and risks of overuse.

- **Educational Messages**
  The following messages should be the focus of Phase II of the educational campaign and should also reinforce the messages from Phase I of the educational campaign:
  - You may have noticed that medicines for pain and fever look different than they used to. These changes will help you: know the active ingredient in your medicine, choose the right medicine for your problem, and use the right dose at the right time.
  - It is important to choose and use a medicine with an ingredient for pain or fever only if you have pain or fever.
  - You should not use two medicines that contain the same active ingredient at the same time. All medicines that contain a pain and fever ingredient now have the name of the ingredient on the front of the package where you can see it right away. Look for the word *acetaminophen, NSAID, or aspirin* on the front of your medicine package.
- **Routes of Dissemination**
  - Press Release
  - Drug Safety Board patient information sheet
  - Message from the Surgeon General
  - Major news network health coverage and news magazine coverage

- Report on National Public Radio
- Through formal partnerships with organizations and associations that promote consumer health and education.

Pros:

- Educational campaigns have been successful in the past in changing risky behaviors and decreasing the occurrence of adverse events.
- Much can be accomplished if resources are adequate.

Cons:

- There is limited funding available.
- A campaign addressing APAP overdose and toxicity was initiated in January 2004 and the problem continues.
- An educational campaign may receive complaints from industry if limited to acetaminophen rather than safe use and the risks of misuse of all OTC analgesic active ingredients.
- An educational campaign without regulatory change may have limited impact. Advertising for APAP products, unlimited package sizes, and the multitude of products available on store shelves may undermine education.

11. Research to identify susceptible populations and safe dosing in these populations

The literature suggests that certain populations may be at increased risk for acetaminophen toxicity. Examples might include those who abuse alcohol or who consume more than 3 alcohol drinks daily, patients with fever, malnourished individuals, and patients with liver disease. However, the data is not definitive even with alcohol overuse or abuse, as some researchers assert a lower risk in chronic alcoholic individuals versus individuals who have just recently stopped drinking alcohol.[70] Additional research in identifying populations at increased risk and the safe dosing in these groups is needed.

Pros:

- Research can help identify what populations or clinical situations need a modified dose or avoidance of acetaminophen.
- May help to avoid limiting use of acetaminophen in populations not at risk.

Cons:

- Research is expensive and time-consuming. It may be years before data is available and acetaminophen overdoses will continue unabated.

Summation

The interaction of the educational programs with regulatory changes is very important. Consumer warning research has shown that the more hazardous a consumer perceives a product to be, the more likely the user will look for and read warning information. Product-users are less likely to read warnings on more familiar products or to even look for or notice warning information on such products. Experience and frequency of product use contribute to a person's familiarity with a product, but people may also consider themselves familiar with a product based on: seeing it used, interacting with advertising, or experiencing other products perceived

as similar.[63] One year after full implementation of the regulations governing the OTC Drug Facts label, the NCPIE conducted a survey of 1009 adults and found that 40% of adults consulted the label for active ingredients and 20% looked for information on side effects and other warnings. Consumer warning experts suggest that this low percentage of warning attendance may reflect a widespread consumer belief that any drug sold OTC must be safe and free of any serious side effects. This paper suggests a combined regulatory and educational approach to address the morbidity and mortality associated with unintentional and intentional acetaminophen overdose in the United States. Required changes in the package label information, package size, and package configuration may reduce consumers' familiarity with acetaminophen and encourage consumers to:

- link physical package changes to educational messages and more prominent, redundant warnings
- link warning messages to a desire to comply with labeled directions for use.

Through a multi-faceted intervention, FDA hopes to maintain the benefits of nonprescription acetaminophen availability while minimizing acetaminophen-associated hepatotoxicity in adults and children.

PubMed Search Terms Used

Acetaminophen and pediatric overdose
Acetaminophen toxicity in children
Acetaminophen and pediatric heptatoxicity
Acetaminophen and paracetamol and liver failure
Acetaminophen and paracetamol and hepatotoxicity
Acetaminophen and paracetamol and overdose
Blister packs and compliance
Acetaminophen dosing and children

Appendix A:
APAP Mechanisms of Toxicity, Concomitant Risk Factors, and Inter-Individual Differences

Mechanisms of Toxicity

Acetaminophen itself is not toxic. Cellular injury is caused by its unstable metabolite, N-acetyl-p-benzoquinone imine (NAPQI). NAPQI is normally present in small amounts and is rapidly neutralized by conjugation with glutathione. Toxic levels of NAPQI accumulate when large amounts of substrate are available for metabolism or the metabolism is accelerated by enzyme induction, as in individuals who regularly consumer alcohol or use medications that cause enzyme induction, like anticonvulsants. In these situations, the hepatic pool of glutathione is depleted, permitting accumulation of NAPQI and subsequent hepatotoxicity. Studies suggest that fasting and malnutrition may also be risk factors that lower the threshold for hepatotoxicity.

At therapeutic doses, acetaminophen is predominantly metabolized by glucuronidation (52-57%) and sulfation (30-44%) conjugation reactions with less than 5% of the drug metabolized by oxidation to NAPQI.[64] In clinical situations involving acute or chronic overuse of acetaminophen (whether unintentional or intentional) or concomitant predisposing factors, the glucuonidation process can become overwhelmed, forcing increased acetaminophen metabolism through the oxidative pathway. When this occurs, the reactive acetaminophen metabolite binds to important hepatic intracellular proteins, resulting in cell death. This process creates acetaminophen-protein adducts that are detectable in serum and may serve as a biomarker of acetaminophen toxicity.[65]

The APAP-induced hepatocellular injury results in a prolonged rise in liver-derived transaminase and alkaline phosphatase serum levels.[1] Without timely intervention, fulminant hepatic failure can ensue.[66] When given early in the hepatotoxic process, oral and intravenous N-acetylcysteine are effective in minimizing acetaminophen-induced liver injury. Methionine is approved for treatment of acetaminophen overdose in other countries.

Concomitant Predisposing Factors

In his 2005 review of drug-induced hapatotoxicity, Willis Maddrey states that two important factors determine the likelihood of APAP-induced hepatic injury:

- The amount of NAPQI produced by P450 2E1
- The availability of glutathione as a hepatoprotectant.[7]

Factors that affect the amount of NAPQI include the amount of APAP ingested as well as factors that affect the production of cytochrome P450 2E1 and glutathione. Most researchers agree that hepatic glutathione depletion is the critical trigger for APAP hepatotoxicity. Alcohol use can decrease intracellular glutathione and may possibly increase cytochrome P450 2E1 (actual amounts or amounts relative to glutathione). These conditions lead to an overproduction and inadequate inactivation of NAPQI and increase the likelihood of hepatotoxicity. While nonprescription APAP product labels include a warning against use if the consumers has three or more alcoholic beverages in a day, there is ongoing controversy regarding the dose of

acetaminophen and amount of alcohol ingestion needed to predispose a person to liver injury.[4] There are inter-subject, gender, and ethnic differences in APAP metabolism that may influence an individual's susceptability to hepatic injury with use of therapeutic or supratherapeutic doses of APAP. Additional details may be found in Appendix A.

Inter-individual differences in susceptability to APAP-associated hepatic injury

There are inter-subject, gender, and ethnic differences in paracetamol metabolism that may influence an individual's susceptability to hepatic injury with use of therapeutic or supratherapeutic doses of acetaminophen.

- In 1986, Critchley et al studied the 24 hour urinary excretion of acetaminophen and its metabolites in 111 Scottish Caucasians, 67 Ghanese (West Africa), and 20 Kenyans (East Africa). Compared to Caucasians, Africans had a statistically significantly lower recovery of mercapturic acid and cysteine conjugates from the urine, suggesting a reduced metabolic activation of paracetamol (production of NAPQI) (5.2% and 4.5% vs. 9.3%, $p<0.0005$). There was a three fold variation in glucuronide and sulphate conjugation among subjects but a sixty fold variation in metabolic activation of paracetamol.
- In 1992, a study by Patel et al in 125 Caucasians and 33 Asians found no differences between ethnic groups in mean fraction of acetaminophen excreted as glucuronide, but found a bimodal distribution among subjects for extent of glucuronidation and N-acetylation (glutathione-derived conjugates). Critchley et al studied 11 healthy Chinese and nine Caucasians, 21-44 years of age who received a single 20 mg/kg dose of acetaminophen syrup following an overnight fast. They found that Chinese subjects absorbed acetaminophen more rapidly and produced relatively more sulfate conjugates, less glucuronidated conjugates, and less mercaptuic acid and cysteine conjugates. These differences could indicate relative protection against acetaminophen-induced hepatotoxicity for the Chinese individuals compared to Caucasian individuals.
- In 1994, Bock et al randomly selected 194 subjects (98 male, 95 female) to study the impact of gender, oral contraceptive use, smoking, and coffee consumption on the metabolism of acetaminphen. Thirty-eight males and 40 females smoked. The investigators identified a trimodal distribution of subjects: poor metabolizers (8%), extensive metabolizers (11%), and moderate metabolizers (81%). Gender and smoking status significantly affected glucuronidation capacity, which was highest in male smokers and lowest in female nonsmokers.
- In 1994, Whitcomb and Block identified fasting as a risk factor for acetaminophen toxicity based on the depletion of essential cofactors needed for efficient acetaminophen conjugation. Others have studied patients with Gilbert Syndrome who have an inherent defect of UDP-glucuronyltransferase 1A1 (to varying degrees). This genetic variiation leads to decreased APAP glucuronidation and increased production of NAPQI compared to normal subjects. These individuals are believed to have an increased risk of acetaminophen-induced hepatotoxicity.

In 2001, Court et al aimed to characterize inter-individual variability in acetaminophen glucuronidation at a therapeutic serum concentration of drug (0.5 mM) and a supratherapeutic concentration that saturated the glucuronidation mechanism (50 mM). The researchers utilized an in-vitro preparation of human liver microsomes obtained from frozen liver samples. The

study found that hepatic microsomal acetaminophen UDP-glucuronosyltransferase (UGT) activities showed a 15-fold inter-individual variability. At least three different UGT isoforms significantly contributed to and mediated the glucuronidation process and their relative contributions changed based on whether the concentration of acetaminophen. Acetaminophen-UGT activity was about 50% higher in livers from male donors compared to livers from female donors.

The following study findings should be considered:

- Healthy individuals develop elevated transaminases levels at maximum therapeutic doses, at least transiently[67]
- Individuals with decreased oral intake and viral illness may develop hepatic injury or failure at therapeutic or mildly supra-therapeutic doses[68]
- Some individuals who regularly use or abuse alcohol may have a lower threshold for acetaminophen toxicity[69,70]
- In vitro-studies on human liver microsomes suggest inter-individual variability in acetaminophen glucuronidation[71,72]
- In-vitro studies on human hepatocytes suggest that exposure of hepatocytes to acetaminophen with either phenytoin or phenobarbitol leads to decreased glucuronidation. This could lead to increased systemic exposure and toxicity for either or both of these drugs.[73] Previously published clinical data on individuals using acetaminophen and either phenytoin or phenobarbitol have been mixed regarding a decreased threshold for acetaminophen hepatotoxicity.

Some individuals with a potentially lower threshold for APAP-induced hepatotoxicity

Appendix B: Summary of Nourjah et al, 2005.

Six surveillance systems used by FDA's Office of Surveillance and Epidemiology to generate national estimates of acetaminophen-associated overdoses (Nourjah et al, 2005)

In preparation for the September 2002 NDAC, FDA reviewers from the Office of Drug Safety (ODS, now OSE) reviewed acetaminophen-associated hepatotoxicity data from national databases and the FDA Adverse Event Reporting System (AERS) to estimate the public health impact of hepatotoxicity in the United States. Drs. Nourjah, Ahmad, Karwoski, and Willy, reviewers later published a study presenting this data. The authors used six different surveillance systems that included data from emergency departments (EDs), hospital discharges, mortality data, poison control centers, and spontaneous postmarketing adverse drug event reports reported to the Food and Drug Administration (FDA):

- National Hospital Ambulatory Medical Care Survey (NHAMCS)
  - The CDC National Center for Health Statistics conducts this survey annually. The survey includes ambulatory care services in hospital EDs and collects information on: demographics of patients, physicians' diagnoses (up to 3), diagnostic/screening services, procedures, medication therapy, disposition, and causes of injury (where applicable). Uses International Classification of Diseases, 9th revision (ICD-9) coding for diagnoses and the ICD code for injuries and poisonings.

- Consumer Product Safety Commission's National Electronic Injury Surveillance System All Injury Program (NEISS)
  - This database collects data on consumer product-related injuries treated in EDs. A sample of 66 hospitals is annually selected to report injury-related information. Data includes: patient demographics, product(s) involved, intentionality, diagnosis, body part affected, ED disposition, incident locale, fire involvement, and work-related injuries. Since 1973, data is included on drug poisonings in children less than six years of age. Starting in July 2000, data on drug injuries for individuals of all ages are included. To retrieve intentionality data, specific drug product names were used to distinguish prescription and nonprescription acetaminophen products.

- National Hospital Discharge Survey (NHDS).
  - CDC conducts this annual survey to characterize inpatients discharged from non-federal short-stay hospitals in the United States. Data includes estimates of patient demographic characteristics, geographic region of hospitals, conditions diagnosed, surgical and non-surgical procedures performed, days of care and length of stay. ICD-9 coding is used.

- National Multiple Cause of Death File
  - Individual States cooperate with the National Center for Health Statistics to provide statistical information from death certificates. The medical information on death certificates is coded according to World Health Organization rules specified in the ICD. Data includes: demographic, geographic, and cause-of-death information. ICD-9 codes were used to search for intentional and unintentional cases of overdose.

- Toxic Exposure Surveillance System (TESS)
  - TESS is a poisoning surveillance database maintained by the American Association of Poison Control Centers in cooperation with more than 60 poison control centers in the United States. Cases included those from the fatal exposures table and the demographic profile of exposure cases table that listed acetaminophen as the primary (first) agent associated with the fatal exposure. Cases were classified as intentional misuse or unintentional overdose.

- FDA Adverse Event Reporting System (AERS)
  - In AERS, the authors conducted a broad search for U.S. cases of hepatic injury reported between 1998 and 2001 with an acetaminophen-containing product as a suspect agent for individuals aged 12 years and older. Cases were excluded if the liver injury was likely attributable to other causes. Cases had to meet one of four predefined case definitions:

    1. non-hospitalized patient with ALT or AST three times the upper limit of normal and total bilirubin at least three times the upper limit of normal or jaundice or INR > 1.5

    2. patient hospitalized or died secondary to an acute liver event.

    The reviewers calculated daily doses based on dosing information provided. If a dose range was provided, the mid-point was used. If the strength of the formulation was unknown, 500 mg strength was used. Cases were categorized as intentional if acetaminophen was used in a suicide attempt or if the patient took a one-time dose of greater than 4 g acetaminophen without a specified indication. Cases were categorized as unintentional if acetaminophen was misused or abused for a therapeutic indication and a suicide attempt was not indicated.

Since each database provided different information in different populations with various degrees of overlap, the results are presented by source. Information from the two databases containing emergency room data is combined.

- ED data (NHAMCS and NEISS):
  From 1993 – 1999, there were an average of 56,000 ED visits per year for APAP-associated overdoses. These visits comprised 7% of all medicinal and biologic substance overdose visits to the ED.
  - 65% of these cases were in individuals between 17 and 64 years of age.
  - 63% of patients were female
  - 56% of were intentional overdoses: 44% suicide attempt, 12% due to use of acetaminophen with other medicines.
  - 23% were unintentional overdoses: 17% accidental ingestions, 6% therapeutic misuse (estimate as based on less than 30 cases)

- Hospital discharges

From 1990 – 1999, there were an average of 26,256 hospitalizations each year for APAP-associated overdoses, which comprised 11% of the total hospital discharges for overdoses with all drugs, medicinal substances, and biologics.

- 74% occurred in individuals between ages 17 and 64 years
- 69% of patients were female
- 74% were intentional overdoses: 33% suicide, 26% APAP and other medicines, 15% suicide and use with other medicinals
- 8% were accidental overdoses that were considered unintentional.

- Mortality files

From 1996 – 1998, there were 1375 deaths (average of 458 per year) identified in which an APAP-associated overdose was either the underlying cause of death or was a contributing cause.

- 1010 records of the 1375 mortality files mentioned suicide or intentional overdose
- 300 records listed the overdose as unintentional
- 65 files indicated unknown intentionality
- 58% of the deceased were females
- 14% were individuals ages 65 years and older
- Among unintentional cases, there was a higher percentage of persons ages 65 years and above (23% vs. 11%)
- Both intentional and unintentional overdoses were more common in females.

- TESS

From 1997 – 2001, there were 112,809 – 119,807 APAP exposures alone or in combination with other products per year. These reports represented about 10% of the 1.2 million pharmaceutical substances exposures reported to TESS each year. During this five year interval, there was little annual variation in number of APAP-associated exposures.

- Of 33,895 APAP exposures in children in 2001, at least 23% involved adult formulations.
- In 2001, nearly 50% of all APAP exposures were unintentional in nature and more than 50% were treated in a health care facility. Two percent of cases involved major effects that were life-threatening or resulted in significant residual disability.
- APAP-associated fatalities represented 16% of the total 1074 fatalities reported to TESS in 2001. About 50% of these fatalities occurred in individuals using a single-ingredient nonprescription APAP product. Ten percent involved multiple APAP products ingested simultaneously.
- In 2001, there were 173 APAP-associated fatalities – almost twice the number of deaths reported to TESS in 1997 (N = 98). Intentional fatalities and unintentional fatalities accounted for 55% and 26% of the total fatalities respectively.

- AERS

From 1998 – 2001, FDA received 759 domestic reports of hepatotoxicity associated with the use of APAP-containing products in individuals ages 12 years and older. Four hundred seventy-eight reports met inclusion criteria, and 70% of these reports were about women. Two hundred (42%) cases or reported hepatotoxicity followed an apparent suicide act, whereas 198 (41%) events appeared unintentional. Among 103 (52% of 278) reports that provided information with which to estimate the daily APAP dose (g/day), 73 (70%) reports suggested that the subject took

more than the maximum recommended APAP dose of 4 g/day. Thirty reports of unintentional overdose with dosing information involved apparent APAP doses of 4 g/day or less.

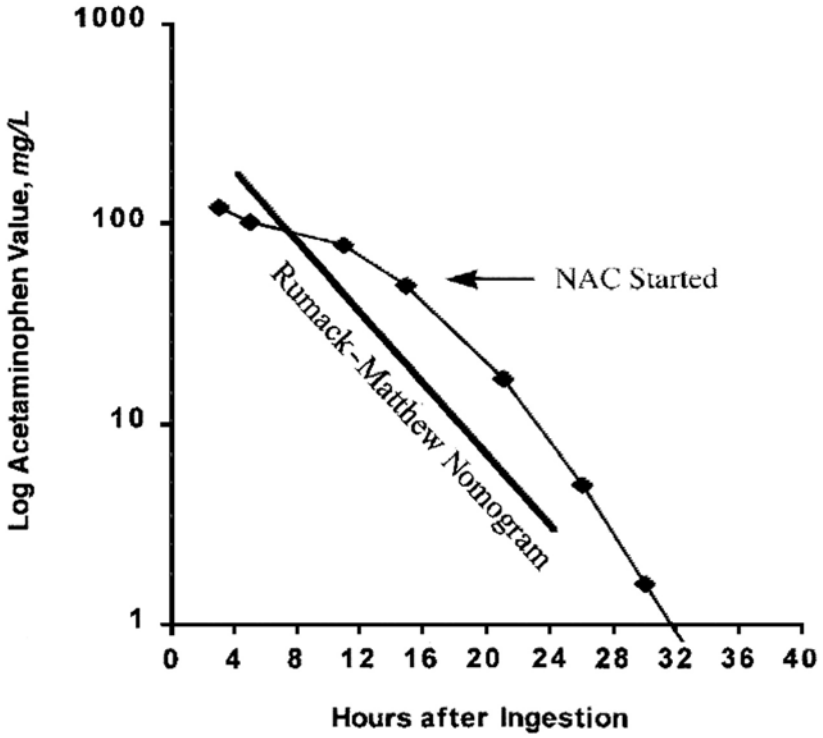
Among the 198 unintentional overdose cases, 170 (86%) reports indicated APAP use for a therapeutic indication, primarily analgesia. The remaining 28 reports involved abuse or misuse of an APAP-containing product, unspecified medication error, or unlabeled use. Among the 170 reports with APAP used for a therapeutic indication, 89 had dosing information with a suggested mean daily dose of 7.5 g. Forty-four reports included noted use of alcohol and 29 cases had a prior history of liver disease. These two subgroups had a mean daily dose of 6.1 g/day and 6.3 g/day respectively. Use of a formulation containing 500 mg of APAP was reported twice as often as use with a 325 mg formulation, and 28% of the 198 unintentional overdose reports suggested use of more than one APAP product – often an OTC product with a prescription product.

The authors acknowledged the following limitations of their database-acquired information:

- Definitions and methodology used to identify cases of APAP-associated overdose and intentionality were different for different databases
- They were unable to review medical records to verify diagnosis and intent
- The time periods of study for each database were inconsistent
- Analyses of data from the databases were limited because of missing information on possible risk factors, details on the consequences of the overdoses (like whether there was liver failure), and missed cases due to attribution errors by healthcare providers.

Despite these limitations, the authors concluded that the large numbers of APAP-associated overdoses identified in national databases suggest misuse or abuse of APAP in the United States population. They acknowledged that certain factors, like concurrent liver disease or alcohol use, may lower the threshold dose of APAP-associated toxicity and measures to reduce the number of APAP-associated overdoses, particularly those due to unintentional misuse, should be considered.

Appendix C:
Application of the Rumack-Matthew nomogram for treating acetaminophen toxicity in a particular case.



Vassalo S, Khan A and Howland MA. Use of the Rumack-Matthew nomogram in cases of extended-release acetaminophen toxicity. Ann Int Med 1996; 125: p.940

Appendix D:
Concepts for PSA's and Other Educational Messages About the Safe Use of OTC Pain and Fever Medicines

- **Title:** Baby Medicine is Not Like Baby Shampoo
  Target Audience: Parents and child care providers

  Message:

  Baby medicine is not like baby shampoo.

  It is not weaker
  It is not gentler
  It is just smaller in size

  Your baby's medicine allows you to give your baby the right amount of medicine based on how much your baby weighs.

  The medicine for your older child does the same.

  More weight, more medicine.
  The right amount based on the size of your child.

  How perfect.

  …Know your child's weight.

- **Title:** Real Men Don't Ask For Directions
  Target Audience: Adolescent boys and men

  Message:

  When it comes to medicines…..asking for directions is cool

  Every over-the-counter medicine label has directions to help you get where you are going – a place where you feel better.

  Follow the directions on your medicine's label. If you don't get to "feeling better" then STOP. Ask for help.

  Maybe you are driving down the wrong road. Your doctor or pharmacist can help you find the medicine that is right for you and your problem.

- **Title:** Get intimate with your pain and fever medicine
  Target audience: All consumers who use OTC pain and fever medicines

  Message:

  How well do you know your pain and fever medicine?

  Not well enough to ignore the directions and warnings.

  No matter how many times you use your pain and fever medicine, it can still hurt you if you use too much.

  Using more acetaminophen than recommended can damage your liver.
  Using more ibuprofen or naproxen sodium than recommended can damage your kidneys.

  Be Smart:

  - Know the active ingredient in your medicine
  - Read the warnings to see if the medicine is right for you and your problem
  - Use the right dose at the right time
  - Measure liquid medicines with a medicine measuring tool
  - If the medicine is not helping you, don't take more. Talk to a healthcare professional about what to do next.

References

[1] Larson AM, Polson J, Fontana RJ, Davern TJ, Lalani E, Lee WM et al. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. Hepatology 2005 Dec;42(6): 1364-1372.

[2] Russo MW, Galanko JA, Shrestha R, Fried MW, Watkins P. Liver Transplantation for Acute Liver Failure From Drug Induced Liver Injury in the United States. Liver Transpl. 2004 Aug; 10(8): 1018-23.

[3] Larson AM, Polson J, Fontana RJ, Davern TJ, Lalani E, Lee WM et al. Acetaminophen sets records in the United States: Number 1 analgesic and number 1 cause of acute liver failure. Hepatology 2005;42: 1364 – 1372.

[4] Kearns GL, Leeder JS, Wasserman GS. Acetaminophen overdose with therapeutic intent [editorial]. J Pediatr 1998; 132:5-8.

[5] 21 CFR 201.322

[6] Nourjah P, Ahmad SR, Karwoski C, Willy M. Estimates of Acetaminophen (Paracetamol)-associated overdoses in the United States. Pharmacoepidemiol Drug Saf. 2006 Jun; 15(6): 398-405.

[7] Gyamlani GG, Parikh CR. Acetaminophen toxicity: suicidal vs accidental. Crit Care. 2002 Apr;6(2):155-9. Epub 2002 Feb 21.

[8] Diagnostic and Statistical Manual of Mental Disorders, 4th edition

[9] Alcohol Abuse and Dependency. ACP Medicine 2006.

[10] Ostapowicz G, Fontana RJ, Schiodt FV, Larson A, Davern TJ et al (Acute Liver Failure Study Group). Results of a Prospective Study of Acute Liver Failure at 17 Tertiary Care Centers in the United States. Ann Intern Med 2002 Dec 17; 137(12):947-54.

[11] Larson AM, Polson J, Fontana RJ, Davern TJ, Lalani E, Lee WM et al. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. Hepatology 2005 Dec;42(6): 1364-1372.

[12] Kerr WC, Midanik L. Generous home-poured alcoholic beverages may lead to overindulgence. Alcoholism: Clinical & Experimental Research 2005 Nov 14;

[13] Carey WD. Acute Liver Failure in the United States. Ann Intern Med. 2003 Dec 16; 139(12): 1044-1045.

[14] Schears RM. Letter to the Editor. Ann Intern Med. 2003 Dec 16; 139(12): 1045.

[15] Lee WM. Acetaminophen and the U.S. Acute Liver Failure Study Group: Lowering the Risks of Hepatic Failure. Hepatology 2004 Jul; 40(1): 6-9.

[16] James L. Updates on the Pathophysiology of Acetaminophen Hepatotoxicity. NIH Acute Liver Failure Workshop 2006 December 4-5. Speaker abstract.

[17] Holubeck WJ, Kalman S, Hoffman RS. Acetaminophen-Induced Actue Liver Failure: Results of a United States Multicenter, Pospective Study. Letter to the editor. Hepatology 2006 Apr;43(4): 880.

[18] O'Grady JG. Broadening the View of Acetaminophen Hepatotoxicity. Hepatology 2005 Dec;42(6):1252 – 1254.

[19] Polson J. Intentional Versus Unintentional Overdoses. NIH Acute Liver Failure Workshop 2006 December 4-5. Speaker abstract.

[20] Gow PJ, Jones RM, Dobson JL, Angus PW. Etiology and outcome of fulminant hepatic failure managed at an Australian liver transplant unit. J Gastroenterol Hepatol. 2004 Feb;19(2):154-9.

[21] Ayonrinde OT, Phelps GJ, Hurley JC, Ayonrinde OA. Paracetamol overdose and hepatotoxicity at a regional Australian hospital: a 4-year experience. Intern Med J. 2005 Nov; 35(11): 655-660.

[22] Watkins PB et al. Aminotransferase Elevations in Healthy Adults Receiving 4 Grams of Acetaminophen Daily. JAMA 2006 Jul 5; 296(1); 87-93.

[23] Bolesta S, Haber SL. Hepatotoxicity associated with chronic acetaminophen administration in patients without risk factors. Ann Pharmacother. 2002 Feb; 36(2): 331-3.

[24] Nahata MC et al. Acetaminophen accumulation in pediatric patients after repeated doses. Eur J Clin Pharmacol. 1984; 27: 57-59.

[25] Kearns GL, Leeder JS, Wasserman GS. Acetaminophen overdose with therapeutic intent [editorial]. J Pediatr 1998; 132:5-8.

[26] Losek JD. Acetaminophen dose accuracy and pediatric emergency care. Ped Emer Care 2004; 20: 285-288.

[27] Muniz AE et al. Unsuspected acetaminophen toxicity in a 58-day-old infant. Ped Emer Care December 2004; 20: 824-828.

[28] Nourjah P, Ahmad SR, Karwoski C, Willy M. Estimates of Acetaminophen (Paracetamol)-associated overdoses in the United States. Pharmacoepidemiol Drug Saf. 2006 Jun; 15(6): 398-405.

[29] Squires RH et al. Acute liver failure in children: the first 348 patients in the pediatric acute liver failure study group. J Pediatr 2006 May;148(5):652-658.

[30] Rumack BH. Acetaminophen overdose in children and adolescents. Pediatr Clin North Am 1986;33:691-701.

[31] Muniz AE, Rose SR, Liner SR, Foster RL. Unsuspected Acetaminophen Toxicity in a 58-day-old Infant. Pediatr Emerg Care. 2004 Dec; 20(12): 824-8.

[32] http://www nlm.nih.gov/medlineplus/ency/article/003430.htm

[33] Yueh-Ping Liu et al. Fulminant hepatic failure due to chronic acetaminophen intoxication in an infant. Amer J Emer Med 2005; 23: 94-95.

[34] Losek JD. Acetaminophen dose accuracy and pediatric emergency care. Ped Emer Care 2004; 20: 285-288.

[35] Bilenko N et al. Determinants of antipyretic misuse in children up to 5 years of age: a cross-sectional study. Clin Ther 2006 May;28(5):783-93.

[36] Lagerlov P, Helseth S, and Holager T. Childhood illnesses and the use of paracetamol (acetaminophen): a qualitative study of parents' management of common childhood illnesses. Fam Pract. 2003 Dec;20(6):717-23.

[37] American Academy of Pediatrics. Committee on Drugs. Acetaminophen toxicity in children. Pediatrics. 2001 Oct;108(4):1020-4.

[38] Gregus Z, Kim HJ, Madhu C, Liu Y, Rozman P, Klaassen CD. Sulfation of acetaminophen and acetaminophen-induced alterations in sulfate and 3_-phosphoadenosine 5_-phosphosulfate homeostasis in rats with deficient dietary intake of sulfur. Drug Metab Dispos. 1994;22:725–730.

[39] O'Shea D, Davis SN, Kim RB, Wilkinson GR. Effect of fasting and obesity in humans on the 6-hydroxylation of chlorzoxazone: a putative probe of CYP2E1 activity. Clin Pharmacol Ther. 1994;56:359–367.

[40] Song BJ, Veech RL, Saenger P. Cytochrome P450IIE1 is elevated in lymphocytes from poorly controlled insulin-dependent diabetics. J Clin Endocrinol Metab. 1990;71:1036–1040.

[41] Dong ZG, Hong JY, Ma QA, et al. Mechanism of induction of cytochrome P-450ac (P-450j) in chemically induced and spontaneously diabetic rats. Arch Biochem Biophys. 1988;263:29–35.

[42] Newgreen DB. Review of nonprescription analgesics—an update. Medicine Evaluations Committee (Australia), April 2003.

[43] Newgreen DB. Review of Non-prescription Analgesics: An update. 2003 Apr. Therapeutic Goods Administration, Medicines Evaluation Committee. Australia.

[44] Lee WM. Acetaminophen and the U.S. Acute Liver Failure Study Group: Lowering the Risks of Hepatic Failure. Hepatology 2004 Jul; 40(1): 6-9.

[45] Hawton K, Ware C, Mistry H, Hewitt J, Kingsbury S et al. Why patients choose paracetamol for self poisoning and their knowledge of its dangers BMJ 1995 Jan 21; 310: 164.

[46] Bernal, W. Personal communication. December 11, 2006.

[47] Morgan O, Majeed A. Restricting paracetamol in the United Kingdom to reduce poisoning: a systemic review. J Public Health 2005 Mar; 27(1): 19-24.

[48] Chan TYK. Improvements in the packaging of drugs and chemicals may reduce the likelihood of severe intentional poisonings in adults. Hum Exp Toxicol. 2000 Jul; 19(7): 387-91.

[49] Lesch MF. Consumer Product Warnings: Research and Recommendations. Handbook of Warnings, Chapter 10. Edited by Michael S. Wogalter. 2006, Lawrence Erlbaum Associates.

[50] PubMed search terms: *blister packs* and *compliance*

[51] Wright JM, Htun Y, Leong MG, Forman P, Ballard RC. Evaluation of the use of calendar blister packaging on patient compliance with STD syndromic treatment regimens. Sex Transm Dis. 1999 Nov;26(10):556-63.

[52] Use of blister packs to improve compliance in renal allograft recipients. Transplantation. 2006 Jul 15;82(1 Suppl 2):825.

[53] Substance Abuse. Women's Health: A Primary Care Clinical Guide, 3rd edition 2004.

[54] Alcohol and the Human Body. http://www.intox.com/physiology.asp

[55] Nabors LA, Lehmkuhl HD, Parkins IS, Drury AM. Reading about over-the-counter medicines. Issues Compr Pediatr Nurs. 2004 Oct-Dec; 27(4): 297-305.

[56] Lesch MF. Consumer Product Warnings: Research and Recommendations. Handbook of Warnings, Chapter 10. Edited by Michael S. Wogalter. 2006, Lawrence Erlbaum Associates.

[57] Wogalter MS, Vigilante WJ. Consumer Product Warnings: Research and Recommendations. Handbook of Warnings, Chapter 18. Edited by Michael S. Wogalter. 2006, Lawrence Erlbaum Associates.

[58] Barrett TW, Norton VC. Parental knowledge of different acetaminophen concentrations for Infants and Children. Academ Emerg Med. 2000 Jun 7; 7(6): 718-21.

[59] John JM. Preventing Medication Errors at Home. J Pharmacy Pract. 2005; 18(3): 141-144.

[60] McMahon SR, Rimsza ME, Bay RC. Parents Can Dose Liquid Medication Accurately. Pediatrics 1997 Sep; 10(3): 330-333.

[61] Frush KS, Luo X, Hutchinsn P, Higgins JN. Evaluation of a Method to Reduce Over-the-Counter Medication Dosing Error. Arch Pediatr Adolesc Med. 2004 Jul; 158: 620-624.

[62] Madlon-Kay DJ, Mosch FS. Liquid Medication Dosing Errors. J Fam Pract. 2000 Aug; 49(8): 741-744.

[63] Handbook of Warnings, Chapters 10, 21. Edited by Michael S. Wogalter. 2006, Lawrence Erlbaum Associates.

[64] Court MH et al. Interindividual Variability in Acetaminophen Glucuronidation by Human Liver Microsomes: Identification of Relevant Acetaminophen UDP-Glucuronsyltransferase Isoforms. J Pharmacol Exp Ther. 2001 Dec; 299(3):998-1006.

[65] Muldrew KL, James LP, Coop L, McCullough SS, Hendrickson HP, Hinson JA, et al. Determination of acetaminophen-protein adducts in mouse liver and serum and human serum after hepatotoxic doses of acetaminophen using high-performance liquid chromatography with electrochemical detec-tion. Drug Metab Dispos 2002;30:446-51.

[66] Maddrey WC. Drug-Induced Hepatotoxicity 2005. J Clin Gastrenterol. 2005 Apr;39(2): S83-S89.

[67] Watkins et al. Aminotransferase Elevations in Healthy Adults Receiving 4 Grams of Acetaminophen Daily. JAMA 2006 Jul 5; 296(1): 87-93.

[68] Whitcomb DC, Block GD. Association of Acetminophen Hepatotoxicity With Fasting and Ethanol Use. JAMA 1994 Dec 21; 272(23): 1845-1850.

[69] Rumack BH. Acetaminophen Misconceptions. Hepatol. 2004 Jul; 40(1): 10-15.

[70] Larson AM et al. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. Hepatology 2005 Dec;42(6): 1364-1372.

[71] Court MH et al. Interindividual Variability in Acetaminophen Glucuronidation by Human Liver Microsomes: Identification of Relevant Acetaminophen UDP-Glucuronosyltransferase Isoforms. J Pharmacol Exp Ther. 2001; 299(3): 998-1006.

[72] Mutlib AE et al. Kinetics of Acetaminophen Glucuronidation by UDP-Glucuronosyltransferases 1A1, 1A6, 1A9 and 2B15. Potential Impliations in Acetaminophen-Induced Hepatotoxicity. Chem Res Toxcol. 2006; 19: 701-709.

[73] Kostrubsky SE et al. Phenobarbital and Phenytoin Increased Acetaminophen Hepatotoxicity Due to Inhibition of UDP-Glucuronosyltransferases in Cultured Human Hepatocytes.

[74] Dassler B. FDA medical officer review of NDA 17-053, Tylenol capsules 500 mg. Feb 20, 1973.

[75] PDR for Nonprescription Drugs, Dietary Supplements, and Herbs. 2007;757-8. Thompson PDR, Montvale, NJ.

Assessment of the Analgesic Efficacy and Hepatotoxicity of Opioid/Acetaminophen Combination Products

March 12, 2007

Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
US Food and Drug Administration

TABLE OF CONTENTS

EXECUTIVE SUMMARY

Acetaminophen-related hepatotoxicity is a well-known phenomenon. As a percentage of all acute liver failure cases, overdose due to acetaminophen, both in over-the-counter (OTC) products and prescription (Rx) products, has increased from 28% in 1998 to 51% in 2003.

This review provides an evaluation of the available data on the analgesic efficacy of the acetaminophen (APAP) component of opioid/APAP combination products, the hepatotoxicity related to the APAP component in the products, as well as prescription patterns (which clinical specialties are prescribing the products and for which indications). Options are presented with respect to potential regulatory actions that could be pursued regarding these combination products.

All opioid/APAP combination products on the U.S. market, except for tramadol/APAP combination (Ultracet®), were approved for *the relief of moderate to moderately severe pain.* Ultracet® is approved for the short-term management of acute pain, with therapy limited to no more than 5 days. Recently published guidelines by the American Pain Society for the management of pain due to malignancies (in 2005) and by the American Society of Interventional Pain Physicians for chronic pain due to other etiologies (in 2006), and the profile of dispensed prescriptions from Verispan Vector One databases, indicate that opioid/APAP combination products are being extensively prescribed for both acute and chronic pain, including pain due to malignancies and pain due to other diagnoses, such as post-surgical pain, back pain, or joint pain (including osteoarthritis). Hydrocodone/APAP combination products are the most commonly prescribed opioid analgesic.

There are only a few reports in the medical literature that assess the analgesic efficacy of opioid/APAP combination products, particularly with factorial design studies that would evaluate the analgesic superiority of the combination over its individual components. Only four full-factorial design studies have been identified: one each of hydrocodone/APAP and oxycodone/APAP and two of codeine/APAP. There were more than 30 partial-factorial design studies of codeine and propoxyphene with APAP. All of these studies were conducted in acute pain populations comparing the combination with only one of the individual components; none were conducted in a patient population experiencing chronic pain.

According to the 2005 report from the U.S. Acute Live Failure Study Group, the opioid/APAP combination products significantly contributed to APAP overdose and hepatotoxicity, particularly the hydrocodone/APAP combination. The number of opioid/APAP-related acute liver failure cases identified by this study group was similar to the number of cases associated with OTC APAP products. The majority of the opioid/APAP-related acute liver failure cases were due to unintentional APAP overdose. It is unknown if the opioid/APAP-related APAP overdose cases were associated with the development of tolerance to and dependence on the opioid component of the combination products.

The Office of Surveillance and Epidemiology (OSE) has performed analyses of various post-marketing surveillance databases and has found data suggesting that use of the opioid/APAP combination products are implicated in APAP overdose, hepatotoxicity and/or death. However, the databases were unable to determine the potential role of opioid dependence and tolerance on the observed toxicities.

Synthesis of the information available from product utilization databases and treatment guideline publications, the available evidence on the efficacy of the combination products in the literature, reports from study groups like the U.S. Acute Liver Failure Study Group, and the post-marketing surveillance databases, has resulted in the following conclusions:

1. Opioid/APAP combination products are extensively prescribed for both, acute to chronic pain, due to a variety of pathological processes.

2. There is a suggestion in the literature that APAP in combination with codeine, hydrocodone or oxycodone, but not propoxyphene, results in analgesic superiority to the individual components for acute pain. However, the strength of the data to support an overall conclusion on the utility of the combination products is limited due the fact that the designs of the studies were suboptimal and chronic pain models have not been evaluated.

3. Opioid/APAP combination products clearly play a role in both intentional and unintentional APAP overdoses and related hepatotoxicity. However, it is not clear what role the development of tolerance to and/or physical dependence upon the opioid component in the combination products plays in these cases.

When all these factors are taken together, it is difficult to conclude with certainty that the overall benefit of combining acetaminophen with opioids in fixed-dose combination products outweighs the risk.

The following options are some of the possible strategies that may be able to address this concern. The options are listed in the order of increasing complexity; they are not mutually exclusive since it is likely that any successful strategy will require a multi-faceted approach.

1. ***Educational outreach***
   The majority of the opioid/APAP-related acute liver failure cases reported by the Acute Liver Failure Study Group were due to unintentional APAP overdose. Some of the cases reported the use of multiple APAP-containing products, including concomitant OTC preparations. Increased awareness of APAP content in products by both health care professionals and patients is needed and such educational efforts may reduce the possibility APAP overdose. Advertisements in the traditional media (television, radio, and periodicals), as well as educational activities through the internet, professional conferences, or continuing medical education (CME) activities, may be useful.

It is noted that previous outreach programs have been conducted and they have had variable success. However, there are new methods such as the FDA information sheets which may make additional efforts worthwhile. However, it should be acknowledged that an educational approach alone is not enough. It will need to be combined with whatever other strategies are implemented and, conversely, any other strategy will have a greater chance of success if it is combined with an educational outreach component that brings attention to and explains the purpose of that particular strategy.

2. ***Labeling modification***
   The package insert of all opioid/APAP combination products may be modified to include a boxed warning to increase awareness by the health care professionals (who will then, theoretically also inform patients).

3. ***Medication guide***
   The creation of a medication guide may reduce the potential for APAP overdose from multiple products by increasing the likelihood that the information is being conveyed to patients.

   As it has been reported that the majority of the unintentional overdoses have been due to patients taking multiple APAP-containing products, both OTC-preparations and prescription products, a medication guide could be strong a counterpart to the educational outreach efforts that are ongoing with the OTC products.

4. ***Reduction of the amount of APAP in the combination***
   Reformulation of the combination products so that the APAP component is only 325 mg (from the current 750 mg that can be found in certain formulations) may reduce the risk of unintentional overdose.

5. ***Uncoupling the components of the opioid/APAP combination products***
   Reformulation of the combination products so that the APAP component is completely eliminated will avoid APAP-related toxicities and overdoses associated with the fixed-dose combinations. However, the 4 most commonly prescribed opioid products are APAP combination products. Whether this is due to prescriber familiarity with these products, patient preference, convenience due to their Controlled Substances Act scheduling designation, or other reasons is unclear.

   It is worth noting that, per the CDER Orange Book, there are currently no approved single entity products for codeine on the U.S. market. Hydrocodone-only products available in the U.S. are formulated with a low dose of homatropine (to discourage deliberate overdosage) but are not indicated for analgesia. These products are approved for the symptomatic relief of cough, and are classified as Schedule III. Another single entity opioid product is propoxyphene, marketed in U.S. as an analgesic; it is a Schedule IV product, but it constitutes less than 5% of the prescriptions dispensed.

Although there are several approved single-entity opioid oral products (oycodone, hydromorphone, oxymorphone, fentanyl, and morphine), they may not be adequate substitutions for a patient whose pain management has been stable on the combination products for several reasons. Theses products differ from the combination products in potency, safety and tolerability profiles, and schedule designation.

There are few alternative products for physicians to prescribe under Schedule III. Codeine combinations with acetaminophen or aspirin are not as frequently prescribed as hydrocodone combination products, perhaps due to a perception of decreased efficacy and more adverse events, although there are little data to quantify these effects. Although morphine products in combination would be prescribed under Schedule III, currently there aren't any morphine combination products approved in the U.S.

Analgesics that are classified as Schedule IV, such as butorphanol, dextropropoxyphene and pentazocine, as well as unscheduled products, such as tramadol, are generally recognized to be less effective for moderate to severe pain than hydrocodone and the opioids prescribed classified as Schedule II.

Aside from the issue of needing to see their prescribers more often in order to get prescription refills which, although it may appear as a minor inconvenience, may actually be a major impediment for some patients, it is likely that that removal of these combination products will have some patients turning to other products. Nonsteroidal anti-inflammatory drugs (NSAIDs) are generally not sufficient for acute postoperative pain, however, they are considered as the first step in analgesic therapy for chronic pain, to be followed by opioids, alone or in combination, once greater analgesia is required. Hydrocodone/ibuprofen and hydrocodone/aspirin combination products are available under Schedule III, but they, like the NSAIDs, each have their own safety issues.

Therefore, reformulation of the opioid/APAP combination products to remove the acetaminophen will significantly impact the pain management options for those patients who have been, or may be, well-managed with opioid/APAP combination products.

BACKGROUND

Acetaminophen (APAP)-related hepatotoxicity is well known and the percentage of the reports of acute liver failure associated with an overdose of an APAP-containing product, both over the counter (OTC) and prescription (Rx) formulations, has increased from 28% in 1998 to 51% in 2003. Opioid/APAP combination products, the only prescription APAP products on U.S. market, have been the source of increased concern after the U.S. Acute Liver Failure Study Group reported their findings in 2005 that more than 50% of APAP-related acute liver failure cases were related to opioid/APAP combination products.

This review provides an evaluation of the role of opioid/APAP combination products in pain management, an assessment of the available data on the analgesic effects of the combination compared to its individual components, a summary of the APAP-related hepatotoxicity associated with the opioid/APAP combination products, and options for potential regulatory actions that could be pursued regarding these combination products.

PAIN MANAGEMENT PRACTICES

Role of Opioid/APAP Combination in Pain Management

Approved Indication

Except for the tramadol/APAP (Ultracet®) combination product, all opioid/APAP combination products have been approved for *the relief of moderate to moderately severe pain,* with the dosing recommendations limiting the maximum APAP dose to 4 grams per 24 hours. These combinations products have been used for pharmacologic management of acute pain and chronic pain, including cancer and non-cancer pain. Ultracet® was approved for the short-term (≤ 5 days) management of acute pain.

Clinical Practice

In the *Guideline for the Management of Cancer Pain in Adults and Children* (published by the American Pain Society in 2005)[i], APAP combinations with hydrocodone, codeine, or oxycodone are recommended for the management of mild to moderate persistent pain due to cancer in adults and children. According to the guidelines, there was strong evidence for the use of opioid analgesics to treat cancer pain on an around-the-clock basis and/or as-needed base; however, the guidelines did not address the strength and consistency of the data to support the use of opioid/APAP combination products for this indication.

For the patient with chronic pain due to a non-cancer etiology, there is little solid evidence in the literature to support the use of opioid combination with APAP. As per the *Opioid Guidelines in the Management of Chronic Non-Cancer Pain*[1], as many as 90% of patients in pain management settings have been reported to receive opioids for chronic

[i] Miaskowski c et al: American Pain Society (APS) 2005, 166p (Clinical Practice Guideline, No. 3), http://www.ampainsoc.org/

pain. Hydrocodone combinations with acetaminophen or ibuprofen were the most commonly used opioid analgesic for treatment of chronic pain. However, the strength of available evidence from the literature to support opioid use for chronic pain was *Limited, Level IV*. Although the guideline did not make particular recommendations on individual opioid analgesics for chronic pain, the *Ten Step Process: An Algorithmic Approach for Long-Term Opioid Therapy in Chronic Pain* was recommended, which includes a comprehensive initial evaluation and diagnosis, risk-benefit assessment, dose adjustment, and monitoring for adverse reaction and abuse.

Pharmacological Rationale

Pharmacologically, opioids and APAP mediate analgesic effects through different mechanisms of action. Opioid analgesics are μ-opiate receptor agonists that work through changes in the perception of pain at the spinal cord and, through higher centers in the central nervous system, an alteration of the emotional response to painful stimuli.[2] APAP is also considered a centrally acting analgesic, although its mechanism of action is not completely clear. Recent studies suggest that APAP selectively inhibits the peroxidase active site of COX-1 and COX-2 (prostaglandin H2 synthases 1 and 2) in neurons and vascular endothelial cells but not in platelets and inflammatory cells.[3] This cellular selectivity of COX inhibition results in analgesic and antipyretic effects for APAP with little anti-platelet and anti-inflammatory activities.

Several review articles discuss the *pharmacological* rationale of the analgesic combination[4-7]. The combination of opioids with APAP may have the following advantages for the treatment of pain:

- Increased analgesic effects: additive or synergetic analgesic effects through a combination of actions that relieve pain by different pharmacological mechanisms.
- Decreased adverse reactions: lower doses of individual components in the combination which may reduce dose-dependent adverse drug reactions (incidence and/or severity).
- Increased compliance: the convenience of taking the combination products (reduced the number of pills and simplified dosing schedule).

However, there is limited clinical evidence in the literature to support the above rationales. There were no efficacy and safety data submitted for review during the approval process of any of the opioid/APAP combination products, except for tramadol/APAP (Ultracet®, NDA 21-123, approved in 2001), due to historical precedence and the different requirements of the 505(j) application process.

Usage of Opioid/APAP Combination Products

Currently, there are approximately 250 approved opioid/APAP combination products marketed in the U.S., as listed in Appendix #1. The hydrocodone/APAP combinations are at the top of the list (n=106 products), followed by oxycodone/APAP (n=44), codeine/APAP (n=40) and propoxyphene/APAP (n=22). The majority of these opioid/APAP combination products were approved under the ANDA (n=247) regulations,

with only four being approved as NDAs. Among the four NDA products, the propoxyphene/APAP combination was approved prior to January 1, 1982 (NDA 17-122), the pentazocine/APAP combination was approved on September 23, 1982 (NDA 18-415), the codeine/APAP/butalbital/caffeine combination was approved on July 30, 1992 (NDA 20-232) and tramadol/APAP (Ultracet®) was approved on August 15, 2001 (the product was assessed with factorial design studies).

The utilization data for the opioid/APAP combination products in U.S. and their indication for use were reviewed by OSE in 2005[ii], 2006[iii] and 2007[iv], as summarized below and Appendices #2 and #3 (also see the OSE reviews for details).

Market Share of Rx vs. OTC APAP products (Appendix #2):
The total sales of APAP products increased from 24.5 billion extended units (tablets/capsules/milliliters of solution) in 2001 to 28.5 billion in 2005 (increased by 17%). Of these, the majority of APAP products were sold as OTC (67% - 61%, slight decrease annually over the four years). The market share of Rx products (opioid/APAP combination) had a slight increase in the yearly proportion from 2001 (33%) to 2005 (39%). The overall sales of opioid/APAP combination products have increased by approximately 38% from an estimated 7.9 million extended units in 2001 to 11 million in 2005. The sales of hydrocodone/APAP combination products nearly doubled from 2001 to 2005 and accounted for 51% in 2001 and 60% in 2005 of the opioid/APAP product market.

Dispensed Rx of opioids vs. opioid/APAP combinations (Appendix #3):
The four most commonly dispensed outpatient prescriptions of opioid analgesics from 2000 to 2005 are hydrocodone, oxycodone, propoxyphene and codeine. The majority of the opioid prescriptions were dispensed as APAP combination: >98% of the hydrocodone, 68-70% of the oxycodone, 96% of the propoxyphene, and 71-76% of the codeine prescriptions.

The number of dispensed prescriptions increased from 2000 to 2005 by 21% in all of the opioid/APAP combination products (14.3 to 17.3 billion units) and by 39% on hydrocodone/APAP combination products (7.5 to 10.4 billion units). Hydrocodone/APAP combination products have been at the top of list since 1997[iii], and in the past 5 years the market share has increased from 53% in 2000 to 60% in 2005. Based of the dispensed prescription data from 2000-2005, the market shares for the other combination products were: oxycodone/APAP increased from 12% to 14%, propoxyphene/APAP decreased from 20% to 13%, and codeine/APAP decreased from 16% to 9%.

[ii] Gita Akhavan-Toyserkani: Postmarketing Safety Review of Hydrocodone Combination (Drug abuse, Dependence, Withdrawal, Overdose, Suicide and Death), OSE Review, Dec 20, 2005
[iii] Laura Governale: OTC and Prescription Combination APAP use. OSE Review, Nov 30, 2006
[iv] Kendra Worthy: Drug Use Review of Acetaminophen (APAP)/Hydrocodone. OSE Review, Jan 23, 2007

Prescription by Patient Age (Appendix #4):
The majority of the dispensed prescriptions for opioid/APAP combination products were for adult, age 17 and above, from 2002 to 2005; the highest counts are for patients between the ages of 41-50 years.

Prescription by Medical Specialty (Appendix #5):
The clinical specialties that prescribed the most opioid/APAP combinations were general practice, internal medicine, dentistry, and orthopedic surgery.

Prescription by Diagnosis (Appendix #6):
Based on the database of Physician Office-Based Practice, the most common diagnoses prescribed hydrocodone/APAP, oxycodone/APAP, and codeine/APAP from 2002 to 2005 were post-surgery follow-up, backache, lumbago and osteoarthrosis.

EFFICACY OF THE OPIOID/APAP COMBINATION

Analgesic Efficacy in Acute Pain

All opioid/APAP combination products, except tramadol/APAP combination (Ultracet®, NDA 21-123), were approved under 505(j) application (ANDA) regulations (see Appendix #1 for list of currently-marketed products in the U.S.). Therefore, no additional efficacy data were submitted to support the superior analgesic effects of the combination compared to its individual components.

Well-controlled data to demonstrate the analgesic superiority of the combination are limited. After an extensive literature search of different databases, a total of four full-factorial design studies (all in acute pain population) were identified: one of hydrocodone/APAP, one of oxycodone/APAP and two of codeine/APAP. There are also a few partial-factorial design studies, which mostly compared the combinations with APAP alone. Overall, the literature suggests that the codeine/APAP combination results in additive analgesia compared to the individual components. However, there is limited evidence in the literature to support the analgesic superiority of APAP combinations with hydrocodone or oxycodone over the individual components.

The following is a brief summary of those factorial design studies. The detailed reviews of the full-factorial design studies and two partial-factorial design studies can been found in Appendix #7. Literature summaries of efficacy studies on opioid/APAP combination products are tabulated in Appendix #8 (hydrocodone/APAP), Appendix #9 (oxycodone/APAP) and Appendix #10 (codeine/APAP).

Factorial design study of hydrocodone/APAP combination
This was a randomized, double-blind, placebo-controlled, full-factorial design study in postpartum patients[8] (See Appendix #7-1 for details). The patients received a single oral

dose of hydrocodone/APAP (10/1000 mg) combination (n=21), hydrocodone (10 mg) alone (n=22), APAP (1000 mg) alone (n=22) or placebo (n=22) followed by 6-hour pain assessment. All treatments were statistically superior to placebo in analgesia outcome measures. Although patients treated with the combination product experienced "additive" pain relief in terms of half-pain relief (with statistical significance versus hydrocodone or APAP alone), the results were not supported by the pain intensity change from baseline and pain relief score.

Factorial design study of oxycodone/APAP combination

One full-factorial design study was published by Cooper, et al, in 1980[9]. It was a randomized, double-blind, 6-arm, single-dose study in post-operative dental pain patients. The patients (37-45 per arm) were treated with oxycodone/APAP combinations (5/500 mg, 5/1000 mg or 10/1000 mg), oxycodone (5 mg), APAP (500 mg) or placebo, followed by a 4-hour analgesic assessment of the following endpoints: pain intensity (PI) and pain relief (PR). All active treatment groups were superior to placebo, per the authors, but statistical significance was not reported. APAP/OX (500/5 mg) in combination was superior to OX (5 mg) or APAP (500 mg) in PI time-course, PR time-course, the sum of pain intensity difference (SPID), 4-hour total pain relief (TOTPAR4), peak PR, time to re-medication, and global impression; however, the statistical significance of the superiority was not reported. There was a trend of a dose-response in pain measures among different combinations with APAP (500-1000 mg) and OX (5-10 mg), but no statistical significance. (See Appendix #7-2 for details).

A partial-factorial design was published in 1996. It was a randomized, double-blind, single-dose study in patients with pain due to abdominal or gynecological surgery [10]. The patients (n=30 per arm) received a single-dose treatment of oxycodone/APAP (10/650 mg), immediate-release oxycodone (15 mg), controlled-release oxycodone (10, 20, or 30 mg) or placebo with a 12-hour post-dosing pain assessment. All active treatments were statistically superior to placebo. Oxycodone/APAP (10/650 mg) in combination tended to be superior to immediate-release oxycodone (15 mg) in PI time-course, PR time-course, SPID, and TOTPAR6, with unreported statistical significance. (See Appendix #7-3 for details).

A meta-analysis published in Cochrane Systemic Review Database pooled efficacy data from seven randomized controlled single-dose trials in acute postoperative pain[11], including the two factorial design trials discussed above[9, 10] ; the remaining five trials used comparisons to placebo. By using descriptor (number-needed-to-treat (NNT) for >50% pain relief) and relative benefit converted from the number of patients with ≥ 50% maxTOTPAR in each trial, the oxycodone/APAP (5/325, 5/500 or 5/1000 mg) combination was superior to placebo. The relative benefit of oxycodone 5 mg over placebo estimated from the Cooper's trial[9] was 1.0 (95% CI: 0.5-2.0), suggesting that addition of APAP to oxycodone 5 mg may result in an additive analgesic effect. However, a firm conclusion would require more studies, particularly in full-factorial design.

Factorial design study of codeine/APAP combination

There were two full-factorial design studies found in the literature[12, 13]. Both were randomized, double-blind, single-dose studies in patients with post-surgical pain. One was in 116 patients with orthopedic or general surgery[13], comparing the analgesic effects of codeine/APAP (60/1000 mg, n=45) with codeine (60 mg, n=23) or APAP (1000 mg, n=45); the other studied 90 male patients after meniscectomy[12], comparing the analgesic effects of codeine/APAP (60/1000 mg) with codeine (60 mg), APAP (1000 mg) or placebo. Overall, the codeine/APAP combination was statistically superior in analgesic effects to codeine but not to APAP in both studies.

The partial-factorial design studies compared the combination with APAP, and lacked a codeine arm, as tabulated in Appendix 10. The codeine/APAP combination showed superiority to APAP (at the same dose) in single-dose acute pain trials. A meta-analysis published in 1997 pooled 13 randomized controlled trials[14] using the number-needed-to-treated (NNT) for ≥50% pain relief as descriptor of analgesic effect across trials and showed additional pain relief with the codeine/APAP combination as compared to APAP. In the same analysis, the authors generated NNT values for codeine 60 mg from other post-operative acute pain trials (with single-patient meta-analysis), which suggests that codeine/APAP combination was superior to APAP or codeine at the same dose in NNT for ≥50% pain relief, without overlapping 95% CI (see Appendix 7-6 for details).

Baseline pain intensity seems to play an important role in determining the sensitivity of analgesic effects in post-operative pain trials. In a randomized placebo-controlled single-dose study in patients with pain due to Caesarean section[15], the additive analgesic effects of the codeine/APAP (60/1000 mg) combination compared to APAP (800 mg) was shown only in patients with severe baseline pain (VAS >60 mm) but not in patients with moderate baseline pain (VAS=40-60 mm). This may explain why the codeine/APAP combination did not show superiority to APAP in the two full-factorial design studies. In these two studies[12, 13] the baseline pain intensity of patients was less than severe (VAS < 60 mm or < 3 on 5-point scale).

Factorial design study of other opioid /APAP combinations

Except for Ultracet® (tramadol 37.5 mg/APAP 325 mg combination, NDA 21-123), all remaining opioid/APAP combination products, including propoxyphene/APAP and pentazocine/APAP combination, were not assessed with full-factorial design studies to support their superior analgesic effects over the individual components at the same dose. There were two meta-analyses with different data processing approaches pooling data from 11 trials in one article[16, 17], and 26 trials in the other[18], on propoxyphene/APAP combination products. All trials were in acute pain and of a randomized controlled design comparing a single-dose of the combination to placebo and/or APAP but not propoxyphene; these were published prior to 1997. It was concluded from both meta-analyses that propoxyphene/APAP combination had no superior analgesic effects over propoxyphene or APAP.

Non-factorial design study of opioid/APAP combinations

There are many randomized controlled studies in the literature that compare the analgesic effects of hydrocodone/APAP combination against placebo in patients with acute pain (see overall summary in Appendix #8). Although an active comparator was included in most studies, neither hydrocodone alone nor APAP alone was studied. The study population was patients with acute pain, such as post-surgical dental pain[19, 20], orthopedic surgery[21-23], sprain[24], or other surgical procedure[25]. Although the results from these studies, which were mostly single oral dose studies, indicate that hydrocodone/APAP combination was superior over placebo for relieving acute pain, it is impossible to conclude that there were any additive analgesic effects of the combination. The tested dose strengths of hydrocodone/APAP combination in the studies were 5/325 mg, 7.5/500 mg, 7.5/650 mg, 7.5/750 mg, 10/650 mg, or 10/100 mg. While 325 – 650 mg APAP is in the lower end of therapeutic level (the generally-accepted therapeutic dose of APAP is 1000 mg), it is undistinguishable if the analgesic superiority demonstrated by the combination was contributed by 5 – 10 mg of hydrocodone. There are no randomized placebo-controlled studies in the literature to demonstrate the analgesic efficacy of a single hydrocodone entity at any dose levels except the above factorial design study[8]. In the Hydrocodone Monograph posted on the Clinical Pharmacology online database[v], the recommended therapeutic dose of hydrocodone for pain relief in adults is 5 – 10 mg every 4 – 6 hours as needed, suggesting that the 5 or 10 mg hydrocodone in the APAP combination may contribute the analgesic effects of the combination.

Analgesic Efficacy in Chronic Pain

The analgesic effects of the opioid/APAP combination in patients with chronic pain have been much less studied. There were no factorial design studies identified in the literature to assess the analgesic superiority of opioid/APAP combination over the individual components in any chronic pain patient population. Randomized controlled studies of opioids for chronic pain in the literature mostly focus on opioid single-entity products other than opioid/APAP combination and only a few studies included a treatment arm of opioid/APAP combination products. Most of these studies were discussed in published systematic reviews in 2004[26] and 2005[27] or meta-analyses in 2006[28] and 2007[29]. However, the evidence level from these studies to support opioids for management of chronic pain is "Limited", as concluded in the *Opioid Guidelines in the Management of Chronic Non-Cancer Pain*[1].

In a meta-analysis[28], 28 randomized placebo-controlled trials of opioids for chronic non-cancer pain (OA, RA, back pain, neuropathic pain or fibromyalgia) were identified. The five opioid analgesics studied in these trials were codeine, oxycodone, propoxyphene, morphine and tramadol. The meta-analysis showed that opioids were more effective than placebo both in pain relief and functional outcome. However, the average duration of treatment was 5 weeks, and mostly ≤ 4 weeks, which is too short to assess analgesic effects in chronic pain. Dropout rates averaged 33% in the opioid treatment group and

[v] Hydrocodone monograph: Clinical Pharmacology online http://www.clinicalpharmacology-ip.com

38% in the placebo control across all studies; the handling of missing data due to dropouts was not specified.

Two studies included in this meta-analysis contained a treatment arm of an opioid/APAP combination. The first was a placebo-controlled 4-week study comparing oxycodone/APAP (5/325 mg) with oxycodone controlled-release (CR, 10 mg) in patients with severe pain due to osteoarthritis.[30] All patients entered a 30-day open-label titration period with oxycodone (immediate release, 5 mg qid) immediately before being randomized to oxycodone/APAP, oxycodone-CR, or placebo. The oxycodone/APAP was superior to placebo in the improvement of pain intensity and sleep quality and comparable to oxycodone-CR at 2 and 4 weeks. However, the study's results were confounded by several factors, such as subjects continuing NSAID therapy during the study and an open-label oxycodone-IR titration period prior to randomization that did not contain a washout period (see Appendix 7-7 for detail).

The second opioid/APAP combination study included in this meta-analysis was a one-week placebo-controlled study of codeine/APAP (30/500 mg) in rheumatoid arthritis patients with moderate-to-severe pain (n=20/arm)[31]. The codeine/APAP combination was statistically superior to placebo in the pain intensity reduced at each time-point and in the 7-day SPID.

In another meta-analysis published this year, 15 studies on opioid treatment for chronic back pain were reviewed[29]. Two of the studies were one-week comparisons between caffeine/APAP (50/500 mg) and propoxyphene/APAP (30/400 mg)[32] and between codeine/APAP (30/500 mg) and tramadol (50 mg)[33]. The analyses did not show pain improvement in favor of the opioid treatment group compared with placebo or a non-opioid control. The authors also pointed out limitations on these studies, including publication bias, poor study quality, and short duration of treatment.

SAFETY OF THE OPIOID/APAP COMBINATION

Hepatotoxicity

APAP in the opioid/APAP combination product has at least the same hepatotoxic profile as APAP single-entity products. There is no clinical evidence to suggest that the opioid in the combination increases the hepatotoxic effects of APAP. However, opioid/APAP combination products, particularly the hydrocodone/APAP combination, contributed approximately half of the acute liver failure cases reported from 22 study centers in the U.S. between 1998 and 2003; most of them were related to unintentional APAP overdose. Since the total use of the prescription opioid/APAP combination products is likely less than APAP products marketed OTC, the incidence of acute liver failure related to opioid/APAP combination products may be much higher.

Drug-Drug Interactions: There are limited data in the literature to evaluate the pharmacokinetic and pharmacodynamic drug-drug interactions between opioids and APAP. Several studies in animals have demonstrated that peripheral or central (intracerebroventricular) administration of morphine, hydromorphone or propoxyphene depletes hepatocellular glutathione[34-38], presumably through stimulation of central μ-opiate receptors. Although hydrocodone was not administered in those studies, its active metabolite, hydromorphone, did have an effect on hepatic glutathione. The mechanism of central effects suggests that depletion of hepatic glutathione is a class effect of opioids. Glutathione is a key factor in the detoxification of NAPQI, (N-acetyl-p-benzoquinone imine), a hepatotoxic metabolite of APAP. Therefore, glutathione depletion by opioids may enhance the APAP-induced hepatotoxicity or decrease the hepatic threshold to APAP toxicity. Interestingly, one other animal study demonstrated that repeated exposure to incremental dose of APAP in mice up-regulated glutathione level and down-regulated hepatic CYP2E1 and CYP1A2 with 4-fold increase in LD50 in response to subsequent lethal dose of APAP[39]. This study suggests that chronic exposure of APAP from opioid combination may attenuate the opioid-induced hepatic glutathione depletion. However, the clinical susceptibility to APAP-associated hepatotoxicity from APAP-opioid as opposed to APAP alone in humans is unknown.

Hepatotoxicity study in healthy subjects

A recently published study (sponsored by Purdue Pharma LP) demonstrated that 1000 mg of APAP in the opioid combination administered every 6 hours for 14 days significantly increased serum ALT in healthy subjects, though the ALT elevation seems comparable to that from APAP alone.[40] The study was a randomized, single-blind, placebo-controlled design to assess the hepatotoxicity of the following four treatment groups: APAP combination with oxycodone, hydromorphone or morphine, and APAP alone. The frequency and magnitude in elevated ALT was comparable across all of the active comparators, suggesting that the opioid component does not increase the hepatotoxicity (at least from the ALT elevation perspective) of the APAP in the combination.

Hydrocodone/APAP combination was not evaluated in the above study but was included in an unpublished study (Study Protocol HXA1017) conducted by the same sponsor (Purdue Pharma LP), and which was submitted to IND 55,965 to support a triple combination product, Hydrocodone/Naltrexone/Acetaminophen (HXA) tablets. In this study healthy adult subjects (n=29/arm) were treated with 2 tablets (1000 mg APAP) of Vicodin (hydrocodone/APAP 5/500 mg), Vicodin/Naltrexone, HXA (5/0.125/500 mg) or placebo every 6 hours for 14 days. Elevations in ALT (>3x ULN) during the study occurred in 45% subjects on Vicodin, 21% on Vicodin/Naltrexone, 17% on HXA and 3% on placebo (see Appendix #11 for details). The IND was later inactivated due to the significant hepatotoxicity.

APAP-related Acute Liver Failure

According to the report by the Acute Liver Failure Study Group in 2005 [41] , 275 (42%) of 662 confirmed acute liver failure (ALF) cases collected from 22 U.S. academic medical centers over a 6-year period (between January 1, 1998 and December 31, 2003) were related to APAP overdose (see Appendix #12 for details). Opioid/APAP combination

products, mostly hydrocodone/APAP, were the major contributors. The majority (69%) of cases of unintentional overdose were due to an overdose of hydrocodone/APAP products.

Among the 275 APAP-related ALF cases:

- 48% (n=131) reported an unintentional overdose
- 44% (n=122) were intentional (suicidal)
- 44% (n=120) took prescription APAP/narcotic combination products
    - 69% (83 of 120) were hydrocodone/APAP combination
    - 63% (83 of 131) were unintentional
    - 18% (22 of 122) were intentional

The report defined *"unintentional"* as *"a multiple-timepoint ingestion to relieve pain or other somatic symptoms with denial of suicidal intent"* and 19% of the patients with unintentional overdose used APAP for > 7 days. However, in the discussion section of the report, the authors stated that "many" of unintentional overdose patients claimed to have ingested modest amounts of APAP over weeks or months. Therefore, the ALF cases due to unintentional overdose of narcotic/APAP combination products were likely from a chronic pain patient population. The authors also commented that the chronic use of APAP or opioid/APAP combination did not seem to cause chronic liver injury.

The authors pointed out that APAP-related ALF cases were probably under-reported in the study due to the exclusion of those cases which lacked informed consent or adequate information to ensure the diagnosis. The 22 study sites represented approximately 30% of U.S. transplant capability and recorded an average of 49 APAP-related ALF cases per year over the 6-year period. They estimated that at least 250 APAP-related ALF cases per year were seen at U.S. transplant centers[41].

However, the study has the following limitations for further risk assessment of opioid/APAP combination-associated hepatotoxicity:

- More characterization of acute liver failure cases associated with opioid/APAP combinations is needed to assess any associations of opioid tolerance and physical dependence with opioid/APAP-related unintentional APAP overdose.
- Unintentional overdose should be further stratified as the "known" overdose (APAP overdose due to seeking more pain relief) and the "unknown" overdose (APAP overdose due to mistaking multiple drugs containing APAP).
- The report did not provide detailed exposure information on the opioid/APAP combination products in the ALF patients, such as duration of treatment, dosage, concurrent medications, clinical indication (acute or chronic pain), history of opioid or APAP use and concomitant medical history (particularly liver disease).
- More detailed comparisons in the APAP-related ALF between OTC and Rx products should be performed, including estimated incidences. While the incidence of APAP-related hepatotoxicity can not be calculated due to unknown actual exposure population (denominator) of acetaminophen OTC and Rx products, the population exposed to OTC products would certainly be much larger than Rx

products based on sales information. Therefore, the hepatotoxicity rate associated with opioid/APAP combination (mostly contributed by hydrocodone/APAP) would likely be higher than with the OTC products.

Spontaneous Reports of APAP-related Hepatotoxicity

A review conducted by OSE[vi] using AERS and other databases suggest that both opioid/APAP combination products and OTC APAP products are associated with APAP overdose, hepatotoxicity or death, as summarized below. However, further analyses may be needed to assess the differences in these APAP-related events between opioid/APAP and OTC APAP products and to estimate whether tolerance to and/or physical dependence on opioids and abuse/misuse of opioids play a critical role in the opioid/APAP-related events.

Overall Profile of APAP-related adverse events (AEs)

1. APAP is currently the number one marketed drug associated with acute liver failure and serious/life-threatening hepatotoxicity in the AERS database.
2. A total 25,237 serious adverse events (SAE) and non-serious AE reports for APAP were identified; 20,252 of them were domestic reports; 28% (5,581 of 20,252) had death as the outcome.
3. APAP-associated AE reports increased yearly, with 4-fold increase during the 9-year period from 1996 to 2005. The number of death reports also quadrupled from 2000 to 2005.
4. APAP was consistently the leading drug on all AE and death reports as compared to other commonly used analgesics from 2000 to 2005.
5. Completed suicide, overdose, coma and hepatic failure were among the most frequently reported AE for APAP when death was listed as an outcome.
6. There is no apparent gender difference in the number of deaths reported: 36% in females, 30% in males and 34% unknown.
7. Death reports were reported most commonly in adults aged 30-50 years.
8. APAP overdose: 6,169 reports (5,148 domestic) and 2,755 suicidal reports (2,407 domestic) in AERS (as of Aug 17, 2006). Of domestic reports, 61% (3,164) of the overdose and 86% (2,080) of suicides had a death outcome. Among overdose cases (from Epidemiologic Data section of the OSE review[vi]):
    a. 63% by OTC products
    b. 37% Rx production
    c. 3% with ≥ 2 APAP products

[vi] Chang YJ et al: OSE Safety Review: Acetaminophen, Hepatotoxicity, Overdose and Death. Feb 5, 2007

APAP-related Hepatotoxicity

1. Based on the OSE MedDRA Reaction Term Groupings "All Liver Events," APAP was listed number one among the top 10 drugs in the cumulative AERS hepatotoxicity reports: 4th in 2002, 3rd in 2003, 1st in 2004, 2nd in 2005 and 1st in 2006.
2. Based on the OSE MedDRA Reaction Term Groupings "Liver Failure", APAP was on 1st among the drugs associated with cumulative and yearly AERS liver failure reports from 2002 to 2006.
3. A total of 4,317 hepatotoxicity reports were identified in the AERS database (as of August 17, 2006), 2,862 of them were domestic reports and 52% (1,501 of 2,862) had a fatal outcome.
4. The domestic hepatotoxicity reports increased yearly since 1990 with 4-fold increase from 1995 to 2005, and the number of deaths reported increased 7-fold during the same time period.
5. The most frequently reported hepatotoxicity-associated terms with APAP were hepatic failure, increased AST and ALT, coma.
6. In an analysis of 100 fatal cases randomly selected from 1,123 APAP-related deaths identified in AERS from Jan 1 to Dec 31, 2005, 72 cases were possibly causally associated with APAP:
   a. 25% hepatic failure or necrosis (n=18), 26% cardiac or respiratory event (n=19), and 49% not reported (n=35).
   b. 67% suicide (n=48), 15% intentional misuse (n=11), 6% unintentional overdose (n=4) and 13% unknown intent (n=9).
   c. 59% on opioid/APAP combo (n=48), 39% on OTC products (n=32), 1% on other Rx combo (n=1)
      i. 65% (31 of 48) of Rx products were intentional overdose (suicide).
      ii. 21% (11 of 48) were unintentional overdose.
      iii. Hydrocodone/APAP combination products were the most frequently reported.
   d. 90% took one APAP product (n=65), 8% used two (n=8), 0% use three and 1% used four.
   e. Most of the cases did not report indication for use.

Abuse and Misuse of Opioid/APAP Combination Products

Although it is generally accepted that chronic users of opioids may develop physical dependence, a small percentage of these patients may also develop tolerance, addiction and subsequent abuse of opioid products. The development of tolerance may result in the patient increasing their dose of the combination product, inadvertently resulting in an overdose of the APAP component. In a recent survey of 335 primary care physicians in Wisconsin on the use of opioids for chronic pain, the most common concerns reported by 248 physician responders (74% of response rate) were "patients abusing the prescription" (84%), "addiction" (75%), "side effects" (68%) and "tolerance built up" (61%).[42] However, there is a paucity of good data in the literature that assess the abuse and misuse of opioid/APAP combination products in the treatment of chronic pain.

A recent study conducted in chronic non-cancer pain with one-year follow-up found that patients initially prescribed hydrocodone/APAP had the highest abuse score compared to tramadol and NSAIDs.[43] In this study, a total of 11,352 patients were enrolled and assigned to one of 3 arms: 3,145 to hydrocodone/APAP, 4,039 to non-selective NSAIDs and 4,168 to tramadol. The prescriptions (containing tramadol, NSAIDs or hydrocodone) were initially randomized to each investigator and once the subject was enrolled, the investigator could prescribe one of three drugs (became non-randomized). The abuse liability was assessed by an "abuse index" with 9 telephone interviews up to one year. The study was funded by Ortho-McNeil Pharmaceutical, the NDA holder for Ultram®, and was submitted to NDA 20-281 (Ultram®) in 2006. The adequacy of the study design, conduct and data analyses is currently under review by the Controlled Substances Staff (CSS).

Abuse liability of opioid analgesics is usually assessed in studies on chronic pain, as discussed in the systematic review articles[26-29]. These trials were not designed to evaluate abuse liability with short observation, less-well designed measures. Very limited information is available to assess tolerance and dependence. The *Opioid Guidelines in the Management of Chronic Non-Cancer Pain*[1] strongly recommends closely monitoring and documenting the abuse liability of patients who are under long-term use of opioid products for management of chronic pain.

OPTIONS

When all these factors are taken together, the overall benefit of fixed-dosed combinations of acetaminophen with opioids is questionable when compared to the risk.

The following options are some of the possible strategies that may be able to address this concern. The options are listed in the order of increasing complexity, and it must be noted that they are not mutually exclusive, since it is likely that any successful strategy will require a multi-faceted approach.

1. ***Educational outreach***

   The majority of the opioid/APAP-related acute liver failure cases reported by the Acute Liver Failure Study Group were due to unintentional APAP overdose. Some of the cases reported the use of multiple APAP-containing products, including concomitant OTC preparations. Increased awareness of APAP content in products by both health care professionals and patients is needed and such educational efforts may reduce the possibility APAP overdose. Advertisements in the traditional media (television, radio, and periodicals), as well as educational opportunities through the internet, professional conferences, or continuing medical education (CME) activities, may be useful.

   It is noted that previous outreach programs have been conducted and they have had variable success. However, there are new methods such as the FDA information

sheets which may make additional efforts worthwhile. However, it should be acknowledged that an educational approach alone is not enough. It will need to be combined with whatever other strategies are implemented and, conversely, any other strategy will have a greater chance of success if it is combined with an educational outreach component that brings attention to and explains the purpose of that particular strategy.

2. ***Labeling modification***

The package insert of all opioid/APAP combination products can be modified to include a boxed warning to highlight the fact that they, as a class, carry a risk of hepatotoxicity. This would be aimed at increasing awareness by the health care professionals (who will then, theoretically also inform patients).

3. ***Medication guide***

The creation of a medication guide may reduce the potential for APAP overdose from multiple products by increasing the likelihood that the information is being conveyed to patients.

As it has been reported that the majority of the unintentional overdoses have been due to patients taking multiple APAP-containing products, both OTC-preparations and prescription products, a medication guide could be strong counterpart to the educational outreach efforts that are ongoing with the OTC products.

4. ***Reduction of the amount of APAP in the combination***

Reformulation of the combination products so that the APAP component is only 325 mg (from the current 750 mg that can be found in certain formulations) may reduce the risk of unintentional overdose.

5. ***Uncoupling the components of the opioid/APAP combination products***

Reformulation of the combination products so that the APAP component is completely eliminated will avoid APAP-related toxicities and overdoses associated with the fixed-dose combinations. However, the 4 most commonly prescribed opioid products are APAP combination products. Whether this is due to prescriber familiarity with these products, patient preference, convenience due to their Controlled Substances Act scheduling designation, or other reasons is unclear.

It is worth noting that, per the CDER Orange Book, there are currently no approved single entity products for codeine on the U.S. market. Hydrocodone-only products available in the U.S. are formulated with a low dose of homatropine (to discourage deliberate overdosage) but are not indicated for analgesia. These products are approved for the symptomatic relief of cough, and are classified as Schedule III. Another single entity opioid product is propoxyphene, marketed in U.S. as an analgesic; it is a Schedule IV product, but it constitutes less than 5% of the prescriptions dispensed.

Although there are several approved single-entity opioid oral products (oycodone, hydromorphone, oxymorphone, fentanyl, and morphine), they may not be adequate substitutions for a patient whose pain management has been stable on the combination products for several reasons. Theses products differ from the combination products in potency, safety and tolerability profiles, and schedule designation.

There are few alternative products for physicians to prescribe under Schedule III. Codeine combinations with acetaminophen or aspirin are not as frequently prescribed as hydrocodone combination products, perhaps due to a perception of decreased efficacy and more adverse events, although there are little data to quantify these effects. Although morphine products in combination would be prescribed under Schedule III, currently there aren't any morphine combination products approved in the U.S.

Analgesics that are classified as Schedule IV, such as butorphanol, dextropropoxyphene and pentazocine, as well as unscheduled products, such as tramadol, are generally recognized to be less effective for moderate to severe pain than hydrocodone and the opioids prescribed classified as Schedule II.

Aside from the issue of needing to see their prescribers more often in order to get prescription refills which, although it may appear as a minor inconvenience, may actually be a major impediment for some patients, it is likely that that removal of these combination products will have some patients turning to other products. Nonsteroidal anti-inflammatory drugs (NSAIDs) are generally not sufficient for acute postoperative pain, however, they are considered as the first step in analgesic therapy for chronic pain, to be followed by opioids, alone or in combination, once greater analgesia is required. Hydrocodone/ibuprofen and hydrocodone/aspirin combination products are available under Schedule III, but they, like the NSAIDs, each have their own safety issues.

Therefore, reformulation of the opioid/APAP combination products to remove the acetaminophen will significantly impact the pain management options for those patients who have been, or may be, well-managed with opioid/APAP combination products.

APPENDICES

Appendix 1. List of Approved Opioid/APAP Combination Products in US

(Extracted from the CDER Orange Book on Jan 22, 2007)

Active Ingredient	Dosage Form	Strength (mg)	Proprietary Name	Indication	Dosage	ANDA	NDA
APAP, ASA, Codeine	Cap	150/180/30	*(generic name only)*			1	0
APAP, Butalbital	Cap Tab	650/50; 325/50	Bucet,, Tencon, Phrenilin, Butapap, Sedapap	Sedapap: Tension headache	1 tab q4h PRN; <6 tab/day	6	0
APAP, Butalbital, Caffeine	Cap Tab Sol	325/50/40 500/50/40 750/50/40 325/50//40 per 15 ml	Esgic-Plus Fioricet			15	0
APAP, Butalbital, Caffeine, Codeine	Cap	325/50/40/30	Phrenilin with Caffeine and Codeine; Fioricet with Codeine			5	1 (20-232)
APAP, Caffeine, Dihydrocodeine	Cap Tab	356.4/30/16 712.8/60/32	*(generic name only)*			3	0
APAP, Codeine (SC-III)	Sol Tab	120/12 per 15 ml 300-650/15-60	Codrix, Tylenol/codeine	Mild-moderately sever pain	≤ 60 mg codeine and ≤ 1 g APAP q4hr	40	0
APAP, Hydrocodone (SC-III)	Cap Tab Sol	300-750/2.5-10, 500/7.7 per 15 ml	Hydrocet, Allay, Lorcet-HD Vicodin, Zydone Anexsia, Lortab Co-Gesic, Norco	Lortab: moderate-moderately severe pain	1-2 tab q4-6h, PRN; <8 tabs per day	106	0
APAP, Oxycodone (SC-II)	Cap Tab Sol	300-650/2.5-10, 325/5 per 5 ml	Tylox, Roxilox Roxicet, OxyIR, Percocet, OxyFast, Oxycet	Percocet: moderate-moderately severe pain	1-2 tab q6h <4g APAP per day	44	0
APAP, Pentazocine (SC-IV)	Tab	650/25	Talacen	Mild-moderate pain	1 caplet q4hr as needed, ≤ 6 caplets/day	2	1 (18-415)
APAP, Propoxyphene HCl (SC-IV)	Tab	650/65	Wygesic			5	
APAP, Propoxyphene Napsylate (SC-IV)	Tab	325-650/50-100	Darvocet	Mild-moderate pain ± fever	100 mg pp/500 mg APAP q4hr as needed, ≤6 tabs/day	17	1 (17-122)
APAP, Tramadol (Un-SC)	Tab	325/37.5	Ultracet	Short-term (≤5 days) tx of acute pain		3	1 (21-123)

Approval dates for the 4 NDAs: NDA 20-232 (July 20, 1992), NDA 18-458 (Sep 23, 1982), NDA 17-122 (< Jan 1, 1982) and NDA 21-123 (Aug 19, 2001); only NDA 21-123 with factorial design study at approval.

Appendix 2. Market Share (Sales) between OTC and Rx APAP Products from Manufacturers to Retail and Non-Retail Channels of Distribution from 2001 to 2005

Laura Governale: OSE review on "OTC and Prescription Combination APAP Use," ***November 30, 2006***

- Total sales increased yearly from 2001 to 2005 for both OTC and Rx APAP products
- Proportion of Rx products increased yearly from 33% to 39%
- Proportion of OTC products decreased yearly from 67% to 61%

Market Setting	Extended Units (x1000)										% Change from 2001 to 2005
	Year 2001		Year 2002		Year 2003		Year 2004		Year 2005		
	N x1000	%	N x1000	%	N x1000	%	N x1000	%	N x1000	%	
Total OTC & Rx	24,460,290	100	25,377,600	100	27,687,155	100	26,193,116	100	28,533,925	100	16.70%
OTC Products	16,486,034	67	16,497,200	65	17,897,267	65	15,895,272	61	17,519,525	61	6.30%
Combination	8,589,645	35	8,628,253	34	9,510,219	34	8,438,389	32	9,743,544	34	13.40%
Single	7,896,389	32	7,868,947	31	8,387,048	30	7,456,883	28	7,775,981	27	-1.50%
Rx Products*	7,974,256	33	8,880,400	35	9,789,889	35	10,297,837	39	11,014,400	39	38.10%

Data are adapted from the Governale's Table 1
The original data source: IMS Health, IMS National Sales Perspectives™, Years 2001 – 2005; Source file: 0609AP01.dvr
† Retail channels include chain, independent, food-store, mail order, discount houses, and mass merchandiser pharmacies in the entire US.
‡ Non-retail channels include hospitals, long-term care facilities, clinics, home health care providers, and HMOs in the entire United States.
* Rx products are all combination products.

Appendix 3. Market Share (Dispensed Prescriptions) among Opioid/APAP Combination Products

Kendra Worthy: OSE Review on "Drug Use review for acetaminophen/hydrocodone," January 23, 2007 and updated by an email on January 26, 2007

- Total dispensed Rx increased yearly for hydrocodone and oxycodone and decreased yearly for propoxyphene and codeine
- The market share (Rx) from high to lower: hydrocodone, propoxyphene, codeine and oxycodone during 2000-2002; hydrocodone, oxycodone, propoxyphene and codeine during 2003-2005
- APAP combination: >98% of hydrocodone, >95% of propoxyphene, 71-77% of codeine, 66%-70% of oxycodone

Opioid Products	Year 2000				Year 2001				Year 2002			
	All Rx#	APAP Combination			All Rx#	APAP Combination			All Rx#	APAP Combination		
		Rx#	% All	% Market		Rx#	% All	% Market		Rx#	% All	% Market
Hydrocodone	76,435,066	74,985,314	98.1	52.6	81,970,478	80,491,856	98.2	54.3	87,457,644	86,080,953	98.4	55.7
Oxycodone	22,356,827	15,268,297	68.3	10.7	25,341,621	16,724,007	66.0	11.3	26,600,350	18,024,970	67.8	11.7
Propoxyphene	29,657,554	28,098,249	94.7	19.7	28,962,679	27,602,680	95.3	18.6	27,051,066	25,859,216	95.6	16.7
Codeine	29,971,097	23,210,381	77.4	16.3	29,061,536	22,126,717	76.1	14.9	26,118,971	19,833,727	75.9	12.8
Tramadol	11,463,131	Not AP			12,308,429	377,132	3.1	0.3	14,346,247	3,999,607	27.9	2.6
Others		988,947		0.7		868,581		0.6		761,803		0.5
Total		142,551,188		100.0		148,190,973		100.0		154,560,276		100.0

Opioid Products	Year 2003				Year 2004				Year 2005			
	All Rx#	APAP Combination			All Rx#	APAP Combination			All Rx#	APAP Combination		
		Rx#	% All	% Market		Rx#	% All	% Market		Rx#	% All	% Market
Hydrocodone	92,365,714	90,890,393	98.4	57.0	97,878,091	96,571,261	98.7	58.4	105,745,988	104,199,284	98.5	60.1
Oxycodone	29,157,681	19,834,591	68.0	12.4	31,229,760	21,728,512	69.6	13.2	34,317,694	24,022,444	70.0	13.8
Propoxyphene	25,943,078	24,924,404	96.1	15.6	24,956,226	23,922,635	95.9	14.5	24,021,891	23,081,684	96.1	13.3
Codeine	25,147,021	18,203,171	72.4	11.4	22,930,124	16,913,236	73.8	10.2	22,392,349	15,923,662	71.1	9.2
Tramadol	15,332,228	4,973,488	32.4	3.1	17,096,274	5,337,060	31.2	3.2	19,153,872	5,508,583	28.8	3.2
Others*		703,859		0.4		762,547		0.5		720,374		0.4
Total*		159,529,906		100.0		165,235,251		100.0		173,456,031		100.0

Data are adapted from Dr. Kendra Worthy's updated tables sent by the email of January 26, 2007.
The original data source: Verispan Vector One™: National, Years 2000-2005, data extracted on 1-26-07
* Others and Total for All Rx of opioid products (single and combination) were not available.

Appendix 4. Age Distribution of Dispensed Prescriptions of Hydrocodone/APAP Combination Products

Kendra Worthy: OSE Review on "Drug Use review for acetaminophen/hydrocodone," January 23, 2007

Table 5: Number of Patients, By Age, Receiving a Prescription for Hydrocodone/APAP Products Through Outpatient Retail Pharmacies from 2002-2005

Age (Years)	2002		2003		2004		2005	
	Patient Count	*Share %*	Patient Count	*Share %*	Patient Count	*Share %*	Patient Count	*Share %*
Grand Total	33,464,137	*100%*	35,518,045	*100%*	36,064,497	*100%*	38,172,533	*100%*
0-5	177,601	*0.53%*	184,318	*0.52%*	177,993	*0.49%*	179,904	*0.47%*
6-11	270,303	*0.81%*	286,958	*0.81%*	279,793	*0.78%*	290,595	*0.76%*
12-16	845,571	*2.53%*	909,110	*2.56%*	938,757	*2.60%*	975,698	*2.56%*
17-20	1,843,216	*5.51%*	1,935,259	*5.45%*	1,975,923	*5.48%*	2,070,115	*5.42%*
21-30	5,302,732	*15.85%*	5,528,563	*15.57%*	5,650,268	*15.67%*	5,793,525	*15.18%*
31-40	6,691,057	*19.99%*	6,780,268	*19.09%*	6,600,180	*18.30%*	6,654,153	*17.43%*
41-50	7,327,792	*21.90%*	7,721,156	*21.74%*	7,719,224	*21.40%*	8,074,042	*21.15%*
51-60	5,313,141	*15.88%*	5,768,137	*16.24%*	5,923,245	*16.42%*	6,546,444	*17.15%*
61-70	3,055,190	*9.13%*	3,370,551	*9.49%*	3,548,635	*9.84%*	3,943,007	*10.33%*
71-80	3,162,374	*9.45%*	3,442,020	*9.69%*	3,580,824	*9.93%*	4,033,274	*10.57%*
Unknown	69,484	*0.21%*	402,474	*1.13%*	658,565	*1.83%*	632,806	*1.66%*

Verispan: Total Patient Tracker (TPT) Data Extracted 1-2007 Source File: TPT 2006-919 Turner-Rinehardt 2006-919 hydrocodone.apap total custom age report.xls

Table 6: Percent Change, by Age, of Patients Receiving a Prescription for Hydrocodone/APAP Products Through Outpatient Retail Pharmacies

Age	2004-2005	2002-2005
Grand Total	5.85%	14.07%
0 - 5 Years	1.07%	1.30%
6 - 11 Years	3.86%	7.51%
12 - 16 Years	3.94%	15.39%
17 - 20 Years	4.77%	12.31%
21 - 30 Years	2.54%	9.26%
31 - 40 Years	0.82%	-0.55%
41 - 50 Years	4.60%	10.18%
51 - 60 Years	10.52%	23.21%
61 - 70 Years	11.11%	29.06%
71+ Years	12.64%	27.54%
Unknown Age	-3.91%	810.72%

Appendix 5. Clinical Specialties Prescribed Opioid/APAP Products

Kendra Worthy: OSE Review on "Drug Use review for acetaminophen/hydrocodone," January 23, 2007

Table 7: Total number of dispensed prescriptions (in thousands) for APAP containing products by prescribing specialty, Years 2002 - 2005

	2002		2003		2004		2005	
	TRxs (000)	*Share %*	TRxs (000)	*Share %*	TRxs (000)	*Share %*	TRxs (000)	*Share %*
TOTAL MARKET	165,578	*100.0%*	169,692	*100.0%*	174,496	*100.0%*	182,287	*100.0%*
hydrocodone/APAP	86,081	*52.0%*	90,890	*53.6%*	96,571	*55.3%*	104,199	*57.2%*
GP/FM/DO	18,657	*21.7%*	20,304	*22.3%*	21,677	*22.4%*	24,305	*23.3%*
IM	10,657	*12.4%*	11,603	*12.8%*	12,380	*12.8%*	13,817	*13.3%*
DENT	11,342	*13.2%*	11,541	*12.7%*	11,894	*12.3%*	12,522	*12.0%*
ORTH SURG	8,974	*10.4%*	9,360	*10.3%*	9,427	*9.8%*	9,979	*9.6%*
UNSPEC	6,667	*7.7%*	6,282	*6.9%*	7,838	*8.1%*	7,308	*7.0%*
EM	5,770	*6.7%*	6,001	*6.6%*	6,035	*6.2%*	6,270	*6.0%*
GEN SURG	2,982	*3.5%*	3,048	*3.4%*	3,090	*3.2%*	3,184	*3.1%*
ANES	1,919	*2.2%*	2,108	*2.3%*	2,268	*2.3%*	2,501	*2.4%*
PA	971	*1.1%*	1,272	*1.4%*	1,688	*1.7%*	2,261	*2.2%*
OB/GYN	2,252	*2.6%*	2,266	*2.5%*	2,198	*2.3%*	2,222	*2.1%*
All Others	15,891	*18.5%*	17,105	*18.8%*	18,076	*18.7%*	19,830	*19.0%*
oxycodone hcl/APAP	18,025	*10.9%*	19,835	*11.7%*	21,728	*12.5%*	24,022	*13.2%*
GP/FM/DO	2,667	*14.8%*	3,097	*15.6%*	3,520	*16.2%*	4,105	*17.1%*
IM	2,061	*11.4%*	2,357	*11.9%*	2,584	*11.9%*	2,945	*12.3%*
ORTH SURG	1,826	*10.1%*	2,007	*10.1%*	2,122	*9.8%*	2,341	*9.7%*
UNSPEC	1,586	*8.8%*	1,566	*7.9%*	1,887	*8.7%*	1,754	*7.3%*
EM	1,245	*6.9%*	1,393	*7.0%*	1,523	*7.0%*	1,743	*7.3%*
DENT	1,351	*7.5%*	1,374	*6.9%*	1,405	*6.5%*	1,500	*6.2%*
OB/GYN	1,134	*6.3%*	1,167	*5.9%*	1,159	*5.3%*	1,229	*5.1%*
GEN SURG	959	*5.3%*	989	*5.0%*	998	*4.6%*	1,041	*4.3%*
AO SURG	695	*3.9%*	733	*3.7%*	765	*3.5%*	823	*3.4%*
ANES	498	*2.8%*	608	*3.1%*	707	*3.3%*	819	*3.4%*
All Others	4,004	*22.2%*	4,543	*22.9%*	5,059	*23.3%*	5,724	*23.8%*
propoxyphene nap/APAP	25,859	*15.6%*	24,924	*14.7%*	23,916	*13.7%*	23,073	*12.7%*
GP/FM/DO	7,010	*27.1%*	6,755	*27.1%*	6,359	*26.6%*	6,310	*27.3%*
IM	4,939	*19.1%*	4,830	*19.4%*	4,582	*19.2%*	4,524	*19.6%*
ORTH SURG	2,346	*9.1%*	2,291	*9.2%*	2,124	*8.9%*	2,018	*8.7%*
UNSPEC	1,985	*7.7%*	1,662	*6.7%*	1,839	*7.7%*	1,526	*6.6%*
DENT	1,319	*5.1%*	1,323	*5.3%*	1,312	*5.5%*	1,266	*5.5%*
OB/GYN	982	*3.8%*	938	*3.8%*	867	*3.6%*	783	*3.4%*
EM	844	*3.3%*	813	*3.3%*	788	*3.3%*	760	*3.3%*
GEN SURG	947	*3.7%*	885	*3.5%*	817	*3.4%*	737	*3.2%*
AO SURG	634	*2.5%*	625	*2.5%*	598	*2.5%*	563	*2.4%*
RHEUM	584	*2.3%*	581	*2.3%*	543	*2.3%*	539	*2.3%*
All Others	4,268	*16.5%*	4,221	*16.9%*	4,086	*17.1%*	4,047	*17.5%*
codeine/APAP	19,834	*12.0%*	18,203	*10.7%*	16,913	*9.7%*	15,924	*8.7%*
GP/FM/DO	3,799	*19.2%*	3,450	*19.0%*	3,127	*18.5%*	3,058	*19.2%*
DENT	3,547	*17.9%*	3,278	*18.0%*	3,047	*18.0%*	2,824	*17.7%*
IM	2,614	*13.2%*	2,381	*13.1%*	2,150	*12.7%*	2,072	*13.0%*
UNSPEC	1,946	*9.8%*	1,715	*9.4%*	1,830	*10.8%*	1,532	*9.6%*
EM	985	*5.0%*	914	*5.0%*	818	*4.8%*	773	*4.9%*
ORTH SURG	964	*4.9%*	865	*4.8%*	757	*4.5%*	693	*4.4%*
OB/GYN	897	*4.5%*	823	*4.5%*	738	*4.4%*	652	*4.1%*
ENT	667	*3.4%*	630	*3.5%*	572	*3.4%*	543	*3.4%*
PED	571	*2.9%*	560	*3.1%*	530	*3.1%*	520	*3.3%*
HOSP	413	*2.1%*	405	*2.2%*	391	*2.3%*	380	*2.4%*
All Others	3,430	*17.3%*	3,182	*17.5%*	2,952	*17.5%*	2,877	*18.1%*

Verispan, VONA, Years 2002 - 2005, Extracted November 2006; Source file: 2006-23 APAP molecule MD.qry

Table 7, continued: Total number of dispensed prescriptions (in thousands) for APAP containing products by prescribing specialty, Years 2002 - 2005

	2002		2003		2004		2005	
	TRxs (000)	*Share* %	TRxs (000)	*Share* %	TRxs (000)	*Share* %	TRxs (000)	*Share* %
tramadol hcl/APAP	4,000	*2.4%*	4,973	*2.9%*	5,337	*3.1%*	5,509	*3.0%*
GP/FM/DO	1,154	*28.8%*	1,404	*28.2%*	1,501	*28.1%*	1,577	*28.6%*
IM	758	*18.9%*	959	*19.3%*	1,059	*19.9%*	1,179	*21.4%*
ORTH SURG	516	*12.9%*	625	*12.6%*	607	*11.4%*	578	*10.5%*
UNSPEC	396	*9.9%*	459	*9.2%*	556	*10.4%*	490	*8.9%*
RHEUM	194	*4.9%*	223	*4.5%*	220	*4.1%*	220	*4.0%*
ANES	129	*3.2%*	160	*3.2%*	172	*3.2%*	166	*3.0%*
EM	132	*3.3%*	162	*3.3%*	158	*3.0%*	154	*2.8%*
PM&R	113	*2.8%*	148	*3.0%*	146	*2.7%*	150	*2.7%*
PA	56	*1.4%*	81	*1.6%*	104	*2.0%*	122	*2.2%*
NP	43	*1.1%*	68	*1.4%*	89	*1.7%*	109	*2.0%*
All Others	510	*12.7%*	683	*13.7%*	724	*13.6%*	763	*13.9%*
APAP/caffeine/butalb	5,410	*3.3%*	5,180	*3.1%*	5,103	*2.9%*	4,738	*2.6%*
GP/FM/DO	1,872	*34.6%*	1,766	*34.1%*	1,704	*33.4%*	1,603	*33.8%*
IM	1,299	*24.0%*	1,280	*24.7%*	1,251	*24.5%*	1,173	*24.8%*
UNSPEC	494	*9.1%*	422	*8.1%*	468	*9.2%*	378	*8.0%*
NEURO	419	*7.7%*	404	*7.8%*	395	*7.7%*	376	*7.9%*
OB/GYN	244	*4.5%*	233	*4.5%*	228	*4.5%*	209	*4.4%*
NP	74	*1.4%*	87	*1.7%*	96	*1.9%*	102	*2.2%*
EM	105	*1.9%*	103	*2.0%*	104	*2.0%*	101	*2.1%*
PA	56	*1.0%*	63	*1.2%*	71	*1.4%*	74	*1.6%*
PED	74	*1.4%*	72	*1.4%*	70	*1.4%*	65	*1.4%*
PSYCH	68	*1.2%*	65	*1.3%*	63	*1.2%*	56	*1.2%*
All Others	705	*13.0%*	685	*13.2%*	653	*12.8%*	600	*12.7%*
acetaminophen	2,856	*1.7%*	2,670	*1.6%*	2,014	*1.2%*	2,202	*1.2%*
PED	776	*27.2%*	708	*26.5%*	498	*24.7%*	597	*27.1%*
UNSPEC	563	*19.7%*	684	*25.6%*	596	*29.6%*	558	*25.3%*
GP/FM/DO	690	*24.2%*	566	*21.2%*	410	*20.3%*	468	*21.3%*
IM	287	*10.1%*	246	*9.2%*	191	*9.5%*	231	*10.5%*
HOSP	99	*3.5%*	83	*3.1%*	59	*2.9%*	59	*2.7%*
EM	65	*2.3%*	64	*2.4%*	42	*2.1%*	48	*2.2%*
NP	49	*1.7%*	42	*1.6%*	30	*1.5%*	38	*1.7%*
PA	18	*0.6%*	23	*0.9%*	18	*0.9%*	28	*1.3%*
DENT	43	*1.5%*	36	*1.4%*	25	*1.3%*	27	*1.2%*
OB/GYN	29	*1.0%*	25	*0.9%*	17	*0.8%*	20	*0.9%*
All Others	237	*8.3%*	192	*7.2%*	129	*6.4%*	128	*5.8%*
All Others	3,513	*2.1%*	3,016	*1.8%*	2,912	*1.7%*	2,619	*1.4%*

Verispan, VONA, Years 2002 - 2005, Extracted November 2006; Source file: 2006-23 APAP molecule MD.qry

Appendix 6. Diagnoses Associated with Prescribing Opioid/APAP Products in Physician Office-Based Practice for Year 2002-2005

Kendra Worthy: OSE Review on "Drug Use review for acetaminophen/hydrocodone," January 23, 2007

Table 8: Top 5 Diagnoses Associated with a Mention of Opioid-APAP Combination Products in Physician Office-Based Practices, 2002-2005 (TRx: Total Rx x 1000)

	2002		2003		2004		2005	
	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*
TOTAL MARKET	81,310	*100.0%*	89,331	*100.0%*	91,923	*100.0%*	93,231	*100.0%*
02232 Codeine & Comb Non-Inj	48,811	*60.0%*	55,166	*61.8%*	59,887	*65.1%*	59,510	*63.8%*
hydrocodone bitartrate/apap	29,321	*60.1%*	34,579	*62.7%*	38,559	*64.4%*	38,227	*64.2%*
V670 surgery follow-up	1,556	*5.3%*	1,809	*5.2%*	2,045	*5.3%*	2,628	*6.9%*
7245 backache NOS	1,453	*5.0%*	1,983	*5.7%*	2,619	*6.8%*	2,268	*5.9%*
7242 lumbago	980	*3.3%*	1,265	*3.7%*	1,247	*3.2%*	1,397	*3.7%*
7194 pain in joint	590	*2.0%*	726	*2.1%*	854	*2.2%*	988	*2.6%*
7159 osteoarthrosis NOS	589	*2.0%*	773	*2.2%*	962	*2.5%*	862	*2.3%*
All Others	24,155	*82.4%*	28,022	*81.0%*	30,832	*80.0%*	30,084	*78.7%*
oxycodone hcl/acetaminophen	8,718	*17.9%*	9,791	*17.7%*	11,272	*18.8%*	12,471	*21.0%*
V670 surgery follow-up	564	*6.5%*	625	*6.4%*	728	*6.5%*	791	*6.3%*
7245 backache NOS	264	*3.0%*	410	*4.2%*	532	*4.7%*	790	*6.3%*
7242 lumbago	203	*2.3%*	183	*1.9%*	323	*2.9%*	578	*4.6%*
5920 calculus of kidney	247	*2.8%*	318	*3.2%*	318	*2.8%*	379	*3.0%*
7159 osteoarthrosis NOS	113	*1.3%*	164	*1.7%*	210	*1.9%*	376	*3.0%*
All Others	7,327	*84.0%*	8,092	*82.6%*	9,161	*81.3%*	9,557	*76.6%*
codeine phosphate/apap	10,705	*21.9%*	10,726	*19.4%*	10,012	*16.7%*	8,719	*14.7%*
V670 surgery follow-up	455	*4.2%*	514	*4.8%*	414	*4.1%*	307	*3.5%*
3540 carpal tunnel syndrome	160	*1.5%*	194	*1.8%*	215	*2.2%*	230	*2.6%*
8450 sprain of ankle	196	*1.8%*	143	*1.3%*	99	*1.0%*	196	*2.2%*
3829 otitis media NOS	224	*2.1%*	133	*1.2%*	162	*1.6%*	191	*2.2%*
7245 backache NOS	295	*2.8%*	354	*3.3%*	337	*3.4%*	178	*2.0%*
All Others	9,376	*87.6%*	9,386	*87.5%*	8,785	*87.7%*	7,617	*87.4%*
All Others	66	*0.1%*	71	*0.1%*	43	*0.1%*	94	*0.2%*
02120 ACETAMINOPHEN	21,578	*26.5%*	23,200	*26.0%*	21,491	*23.4%*	24,059	*25.8%*
acetaminophen	20,169	*93.5%*	22,033	*95.0%*	20,201	*94.0%*	22,742	*94.5%*
4620 acute pharyngitis	1,597	*7.9%*	1,674	*7.6%*	1,488	*7.4%*	1,901	*8.4%*
7806 pyrexia unknown origin	1,182	*5.9%*	1,346	*6.1%*	1,298	*6.4%*	1,528	*6.7%*
4659 acute URI NOS	1,510	*7.5%*	1,585	7.2%	1,403	*6.9%*	1,474	*6.5%*
3829 otitis media NOS	1,259	*6.2%*	1,357	6.2%	1,070	*5.3%*	1,253	*5.5%*
V202 routine child health exam	790	*3.9%*	1,244	5.6%	1,105	*5.5%*	1,114	*4.9%*
All Others	13,831	*68.6%*	14,827	67.3%	13,836	*68.5%*	15,471	*68.0%*
acetaminophen/caffeine/butalb	1,409	*6.5%*	1,167	5.0%	1,289	*6.0%*	1,317	*5.5%*
7840 headache	620	*44.0%*	466	39.9%	486	*37.7%*	517	*39.2%*
3469 migraine NOS	348	*24.7%*	304	26.1%	341	*26.4%*	315	*23.9%*
3078 psychalgia	247	*17.5%*	203	17.4%	274	*21.2%*	293	*22.2%*
7245 backache NOS	10	*0.7%*	24	2.1%	11	*0.9%*	22	*1.6%*
4659 acute URI NOS	--	--	15	1.2%	5	*0.4%*	16	*1.2%*
All Others	184	*13.1%*	155	13.3%	173	*13.4%*	155	*11.8%*

Table 8 (continued):

	2002		2003		2004		2005	
	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*
02212 PROPOXYPHENES	8,738	*10.7%*	8,069	*9.0%*	7,626	*8.3%*	7,089	*7.6%*
propoxyphene napsylate/apap	8,483	*97.1%*	7,758	*96.1%*	7,232	*94.8%*	6,700	*94.5%*
V670 surgery follow-up	414	*4.9%*	348	*4.5%*	299	*4.1%*	366	*5.5%*
7159 osteoarthrosis NOS	377	*4.4%*	338	*4.4%*	270	*3.7%*	304	*4.5%*
7245 backache NOS	525	*6.2%*	448	*5.8%*	445	*6.2%*	243	*3.6%*
7194 pain in joint	255	*3.0%*	192	*2.5%*	231	*3.2%*	239	*3.6%*
7242 lumbago	242	*2.9%*	204	*2.6%*	222	*3.1%*	167	*2.5%*
All Others	6,669	*78.6%*	6,228	*80.3%*	5,766	*79.7%*	5,380	*80.3%*
propoxyphene hcl/acetaminophen	256	*2.9%*	311	*3.9%*	375	*4.9%*	367	*5.2%*
8470 sprain of neck	9	*3.5%*	5	*1.7%*	5	*1.4%*	26	*7.0%*
7245 backache NOS	11	*4.5%*	5	*1.6%*	6	*1.7%*	23	*6.4%*
7890 abdominal pain	7	*2.8%*	--	--	9	*2.3%*	17	*4.6%*
8150 fracture metacarpal, closed	--	--	--	--	--	--	16	*4.4%*
8208 frac. neck of femur NOS, closed	--	--	5	*1.8%*	--	--	16	*4.3%*
All Others	228	*89.3%*	295	*95.0%*	355	*94.6%*	269	*73.3%*
All Others	--	--	--	--	19	*0.2%*	22	*0.3%*
02132 SYN NON-NARC NON-INJ	2,184	*2.7%*	2,889	*3.2%*	2,908	*3.2%*	2,557	*2.7%*
tramadol hcl/acetaminophen	2,184	*100.0%*	2,889	*100.0%*	2,908	*100.0%*	2,557	*100.0%*
7245 backache NOS	116	*5.3%*	218	*7.6%*	252	*8.7%*	216	*8.5%*
7159 osteoarthrosis NOS	111	*5.1%*	226	*7.8%*	144	*4.9%*	188	*7.4%*
7194 pain in joint	106	*4.9%*	96	*3.3%*	115	*4.0%*	164	*6.4%*
7242 lumbago	162	*7.4%*	159	*5.5%*	83	*2.9%*	161	*6.3%*
7840 headache	83	*3.8%*	81	*2.8%*	120	*4.1%*	86	*3.4%*
All Others	1,605	*73.5%*	2,109	*73.0%*	2,194	*75.4%*	1,742	*68.1%*
All Others	--	--	7	*0.0%*	12	*0.0%*	17	*0.0%*

Verispan, Physician Drug and Diagnosis Audit (PDDA): Years 2001 – 2005, Extracted 12/2006. Source file: PDDA 2006-919 Turner-Rinehardt 12-15-06 hydrocodone-apap diag .xls

Appendix 7. Factorial Design Studies

The following are the detailed reviews of 4 full-factorial design studies and 2 partial-factorial design studies.

7-1. Hydrocodone/APAP combination: One full-factorial design study

Beaver WT and McMillan D: Methodological considerations in the evaluation of analgesic combinations: acetaminophen (paracetamol) and hydrocodone in postpartum pain. ***Br J Clin Pharm*** 10: 215S-223S, 1980 [8]

Study design: a randomized, double-blind, placebo-controlled, 2x2 factorial design study

Subjects and Treatment: n=108 postpartum patients with either episiotomy or uterine cramp pain within 48 hours of vaginal delivery. Patients were stratified for initial pain intensity (moderate or severe) and for pain types (episiotomy or uterine cramp) and allocated to each of following treatment group (a single oral dose):

- APAP/Hydrocodone (1000/10 mg), n=21
- Hydrocodone bitartrate 10 mg, n=22
- APAP 1000 mg, n=22
- Codeine phosphate 60 mg, n=22
- Placebo, n=22

Outcome measures

- Pain intensity: 4-point categorical scale: 0=none, 1=little, 2=moderate, 3=severe
- Pain relief: 5-point scale: 0=none, 2=slight, 4=complete
- 50% pain relief: pain at least "half-gone" experienced by patients

Efficacy analysis:

- PID (change in PI from baseline)
- Total effect (AUC by totaling the hourly score for 6 hours)
- Peak effect: the first 3 hours post dosing
- Responder analysis (50% pain relief)

Results:

- No dropouts by the end of the study.
- Hydrocodone/APAP combination, hydrocodone or APAP alone were statistically superior to placebo in analgesic efficacy with a single oral dose in patients with postpartum pain during the 6-hour pain assessment (Figures 1-3, generated from the authors' Table 1).
- The combination was statically superior to hydrocodone or APAP alone in the responder analysis (50% pain relief) (Figure 3) but was not supported by results from analysis of change in pain intensity from baseline and pain relief score (Figures 1 and 2).

Comments

- Inconsistency or mutual support from different pain measures
- Limited data available for statistically analysis

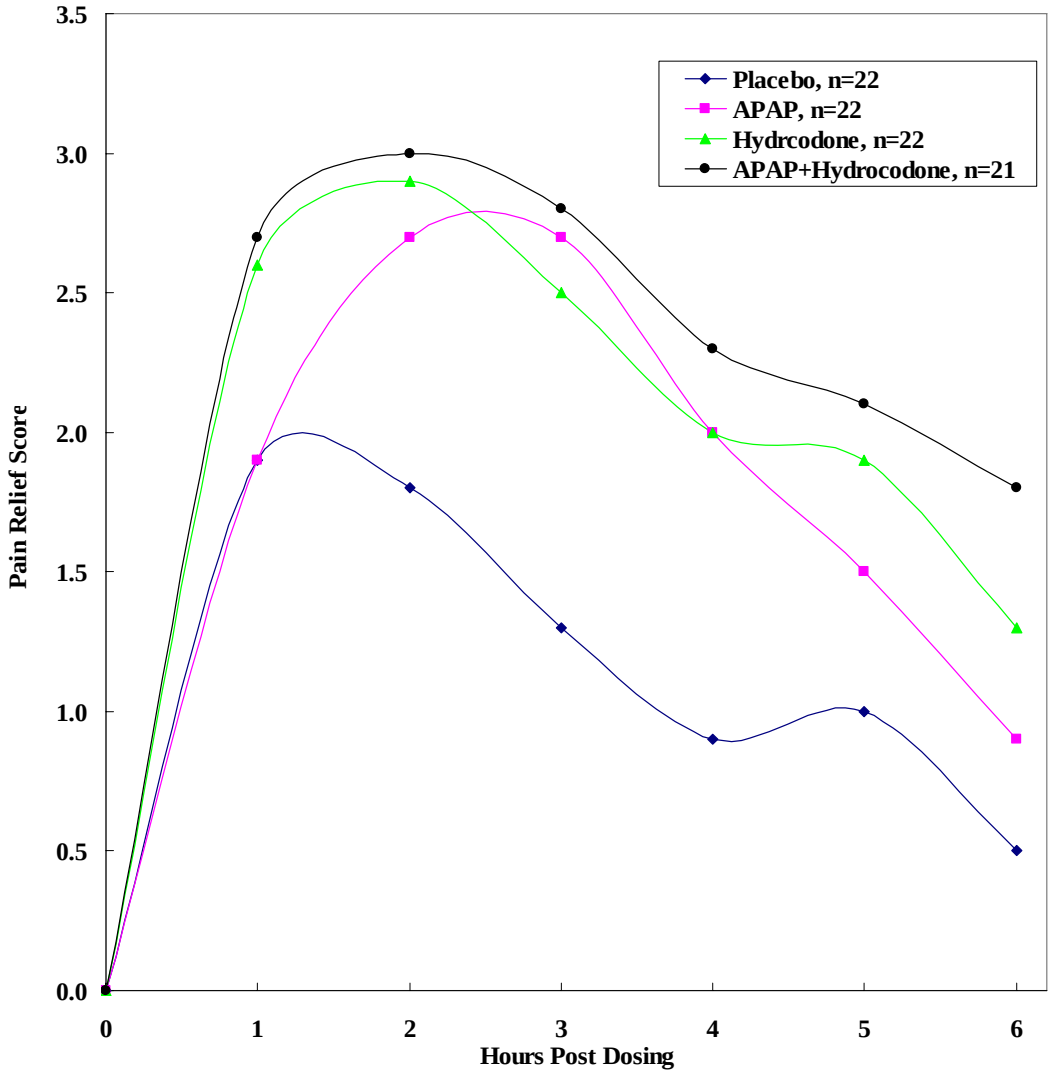


Figure 1. **Time-Course of Pain Relief Scores** in patients with postpartum pain treated with a single oral dose of hydrocodone/APAP combination (10/1000mg), hydrocodone (10 mg) alone, APAP (1000 mg) alone, or placebo. The pain relief was assessed with a 5-point categorical scale (0=none and 4=complete). Data are mean scores at each time point; the standard deviation was not reported in the article. (The figure is generated from the authors' Table 1).

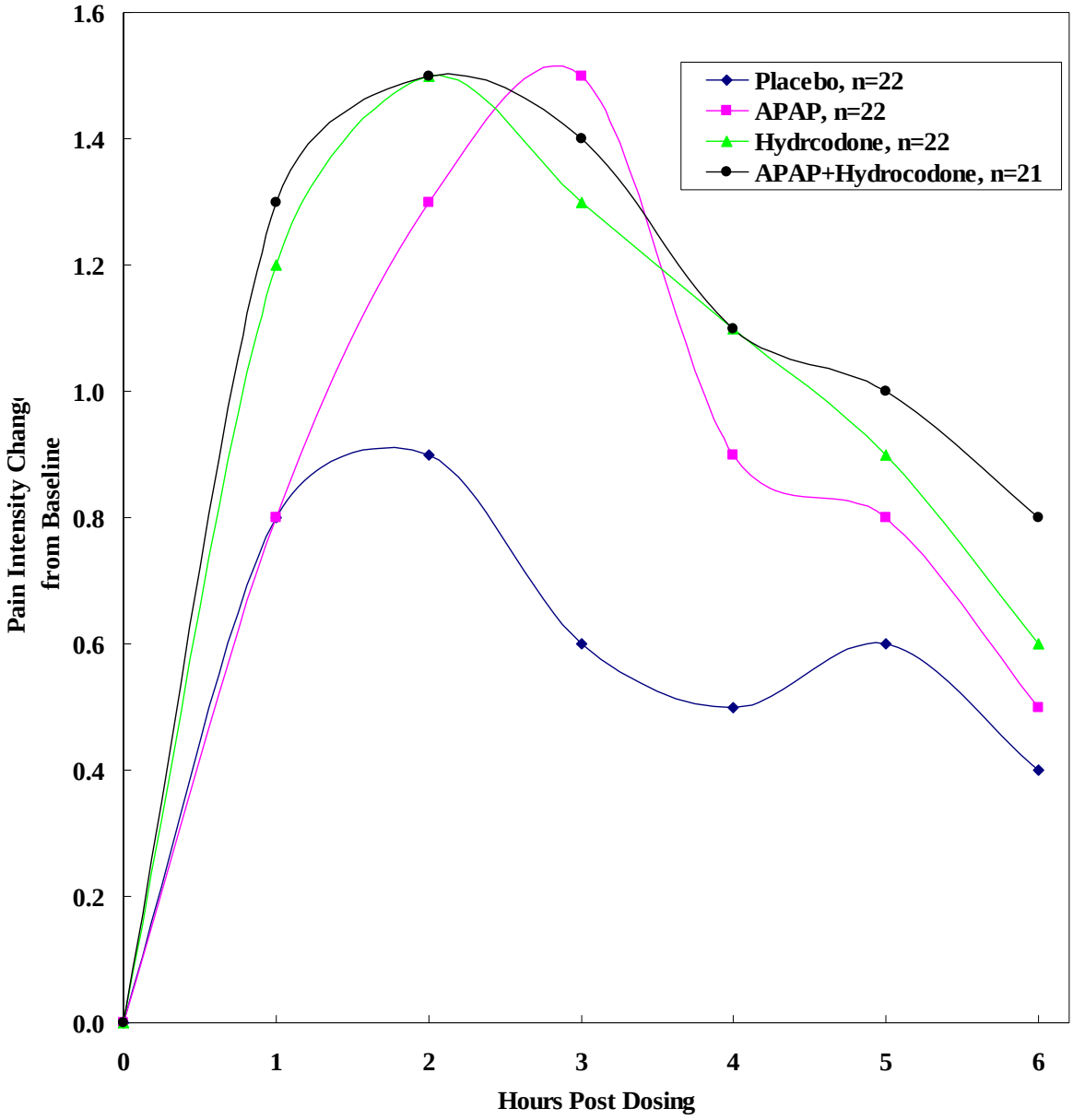


Figure 2. **Time-Course of Change in Pain Intensity from Baseline** in patients with postpartum pain treated with a single oral dose of hydrocodone/APAP combination (10/1000mg), hydrocodone (10 mg) alone, APAP (1000 mg) alone, or placebo. The pain intensity was measured with a 4-point categorical scale (0=none and 3=severe). Data are mean change scores at each time point; the standard deviation was not reported in the article. (The figure is generated from the authors' Table 1).

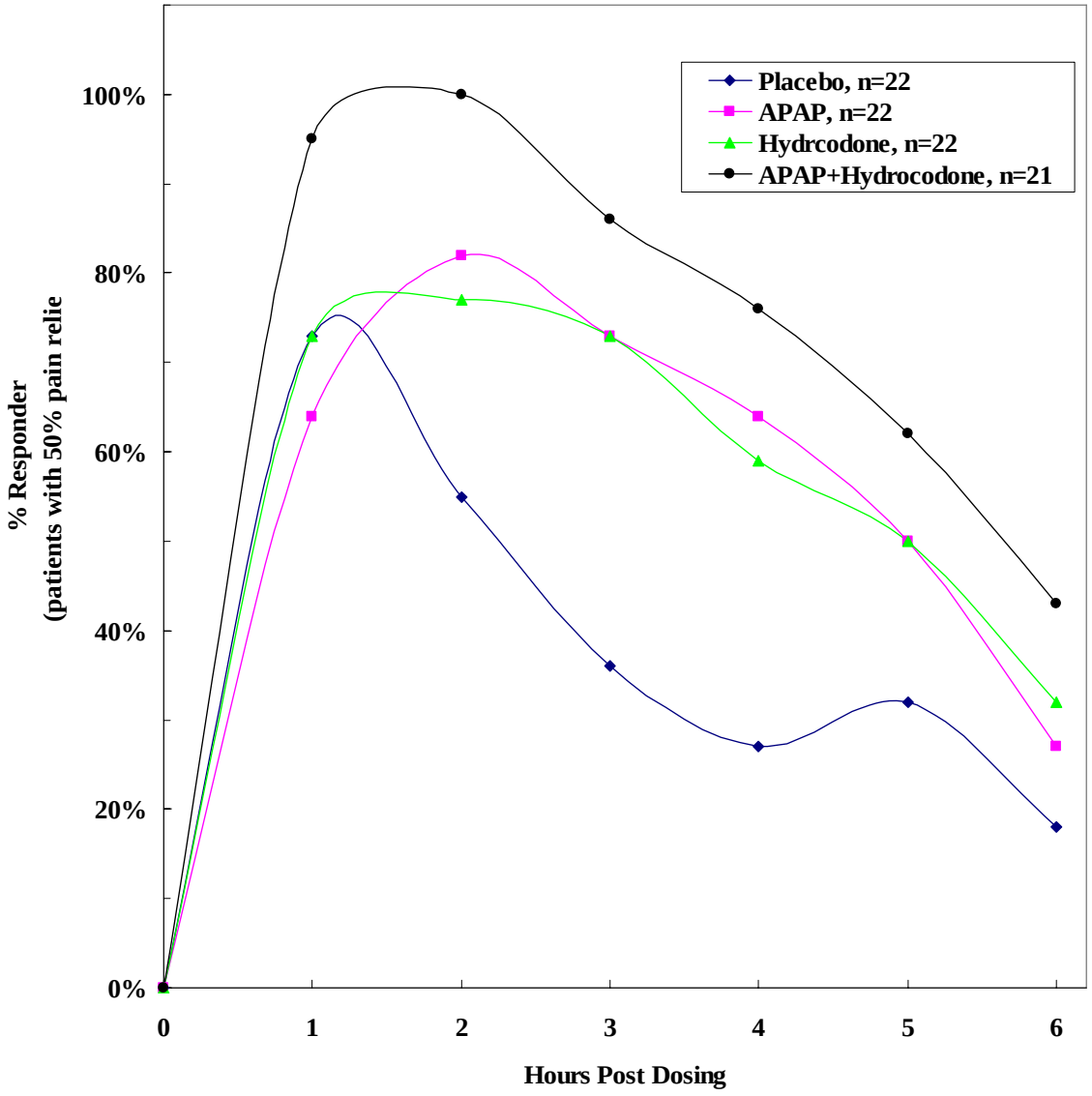


Figure 3. **Time-course of responder** in patients with postpartum pain treated with a single oral dose of hydrocodone/APAP combination (10/1000mg), hydrocodone (10 mg) alone, APAP (1000 mg) alone, or placebo. The responder was defined as patients who reported their pain at least 50% relieved. (The figure is generated from the authors' Table 1).

7-2. Oxycodone/APAP Combination: One full factorial design study

Cooper SA et al: Time-course of analgesia of a single oral dose of oxycodone/APAP combination in post-op dental pain with 2x2 factorial design. ***Oral Surg*** 50(6): 496, 1980 [9]

Design: This was a randomized, double-blind, placebo-controlled, full factorial design, 6-arm, single-dose study in patients with pain from dental surgery.

Subject and Treatment: A total of 298 patients experiencing moderate or severe pain post-surgery were allocated to one of the following 6 treatment groups (a single oral dose):

- Oxycodone/APAP (5/500 mg), n=45
- Oxycodone/APAP (5/1000 mg), n=40
- Oxycodone/APAP (10/1000 mg), n=45
- Oxycodone IR (5 mg), 42
- APAP (500 mg), n=37
- Placebo, n=38

Pain Assessment: hourly for 4 hours post dosing, including PI on 4-point scale, PR on 5-point scale, half pain gone, global impression (5-point). The data were analyzed as SPID, TOPAR, sum total hours with pain at least half relieved.

Results:

- Dropout rate was 17% (51 of 298) by end of the study (n=21 lost to f/u, n=10 withdraw prior to medication, and n=20 protocol violation), but not specified to each tx group. N=247 (298-51) completed the study.
- 47% of patients (n=117 of 247) completed 4-hour evaluation; the remaining patients re-medicated: 26/38 on placebo, 28/42 on Ox 5mg and 25/37 on APAP 500 mg; other groups were not reported.
- All treatments, combinations or single entity, were superior to placebo in analgesia as per the author; but statistical significance is not reported.
- Time-course of analgesic during the 4-hour assessment showed APAP/OX (500/5 mg) combination was superior to OX 5 mg alone and APAP 500 mg in both PI change from baseline (Figure 1) and PR score (Figure 2), however, statistical significance is not reported in the article.
- APAP/OX (500/5 mg) was superior to OX 5 mg or APAP 500 mg in SPID, TOTPAR, peak PR, time to re-medication and global impression (the authors' Table II); but statistical significance is not reported.
- There was a trend of a dose-response in pain measures among different combinations between APAP and OX, but no statistical significance.

Comments:

- Statistical superiority of the combination over OX or APAP is unknown; limited data available in the article for statistical re-analysis
- Self medication after surgical procedure at home

- Only 47% (117 of 247) of patients completed 4-hour assessment; 17% dropouts plus significant subjects re-medicated during the 4 hours.
- Pain assessment data recorded on a diary which was collected within one week.
- Short assessment, 4 hours post dosing.

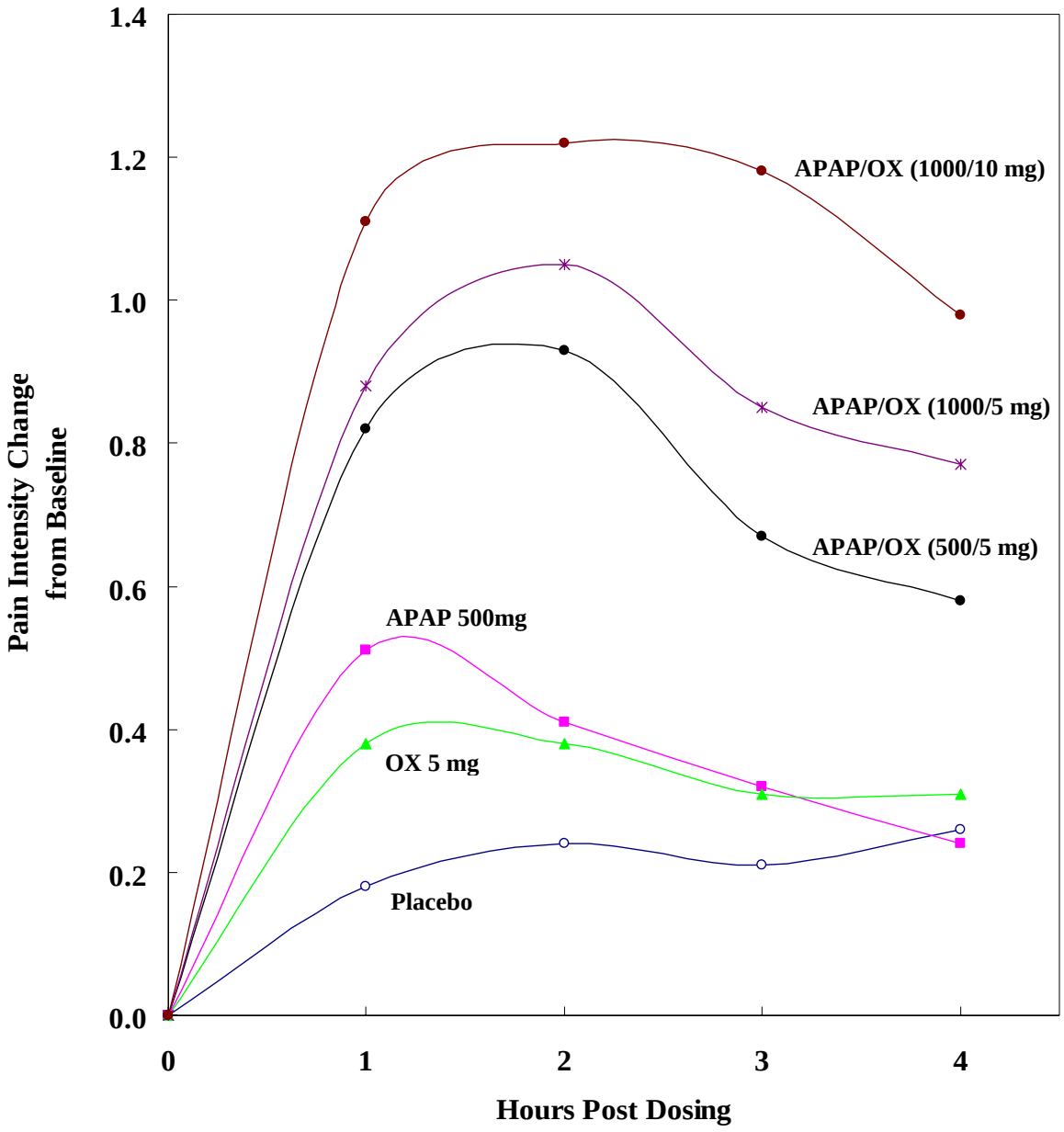


Figure 1. **Time-Course of Change in Pain Intensity from Baseline** in patients with post-surgical dental pain treated with a single oral dose of oxycodone/APAP combination (5/500 mg, 5/1000 mg or 10/1000 mg), oxycodone (5 mg) alone, APAP (500 mg) alone, or placebo. The pain intensity was measured with a 4-point categorical scale (0=none and 3=severe). Data are mean change scores at each time point; the standard deviation was ***not*** reported in the article. Refer to *Figure 2* for legends in next page. (The figure is generated from the authors' Table II).

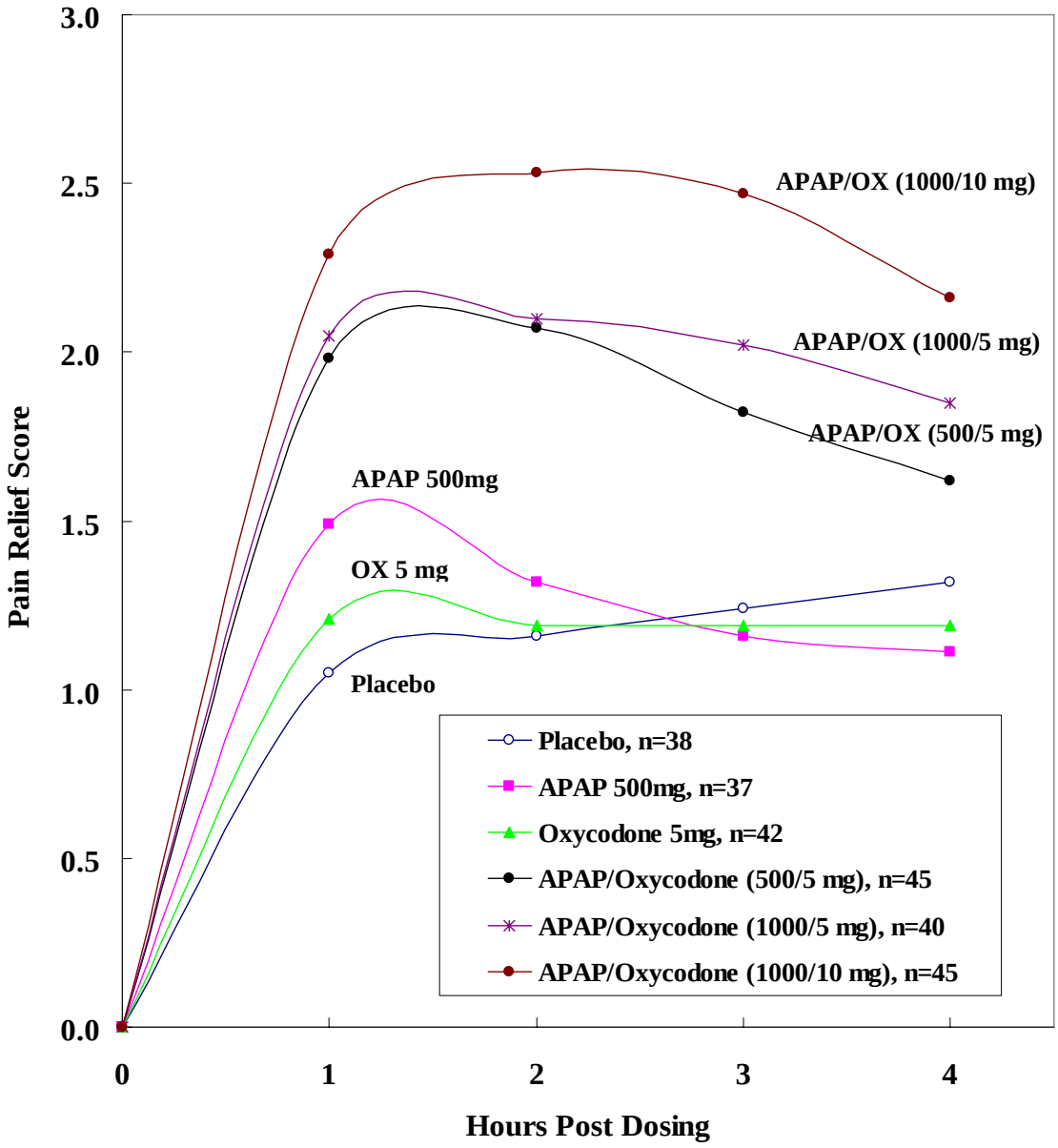


Figure 2. **Time-Course of Pain Relief Scores** in patients with post-surgical dental pain treated with a single oral dose of oxycodone/APAP combination (5/500 mg, 5/1000 mg or 10/1000 mg), oxycodone (5 mg) alone, APAP (500 mg) alone, or placebo. The pain relief was assessed with a 5-point categorical scale (0=none and 4=complete). Data are mean scores at each time point; the standard deviation was ***not*** reported in the article. (The figure is generated from the authors' Table II).

Table II. Summary of analgesic scores

Mean scores	*Placebo*	*Acetaminophen 500 mg.*	*Oxycodone 5 mg.*	*APAP 500 mg. + Oxycodone 5 mg.*	*APAP 1,000 mg. + Oxycodone 5 mg.*	*APAP 1,000 mg. + Oxycodone 10 mg.*
Hourly PID						
1	0.18	0.51	0.38	0.82	0.88	1.11
2	0.24	0.41	0.38	0.93	1.05	1.22
3	0.21	0.32	0.31	0.67	0.85	1.18
4	0.26	0.24	0.31	0.58	0.77	0.98
SPID	0.87	1.49	1.38	3.00	3.55	4.49
Peak PID	0.42	0.68	0.48	1.13	1.30	1.60
Hourly relief						
1	1.05	1.49	1.21	1.98	2.05	2.29
2	1.16	1.32	1.19	2.07	2.10	2.53
3	1.24	1.16	1.19	1.82	2.02	2.47
4	1.32	1.11	1.19	1.62	1.85	2.16
TOTPAR	4.76	5.08	4.79	7.49	8.05	9.44
Peak relief	1.45	1.76	1.50	2.58	2.47	2.93
Observations with pain half-gone	0.63	0.95	1.12	2.00	2.15	2.56
Global evaluation	0.89	0.89	0.88	1.76	1.95	1.96
Time to remedication	152.2	170.6	166.9	211.0	192.6	205.8

7-3. Oxycodone/APAP Combination: A partial-factorial design study-acute pain

Sunshine A et al: analgesic efficacy of controlled-release oxycodone in postoperative pain. ***J Clin Pharmacol*** 36:595-602, 1996 [10]

Design: This was a randomized, double-blind, placebo-controlled, partial factorial design, 6-arm, single-dose study in patients with pain due to abdominal or gynecological surgery.

Subject and Treatment: A total of 180 patients experiencing moderate or severe pain after abdominal or gynecological surgery were allocated to each of 6 groups (n=30 each arm) and received the following single dose treatment:

- Oxycodone/APAP (10/650 mg)
- Oxycodone IR (15 mg)
- Oxycodone CR (10, 20, or 30 mg)
- Placebo

Pain Assessment:

- Hourly for 12 hours post dosing
- PI on 4-point scale, PR on 5-point scale and VAS, onset and duration, overall PR at 12 hr and global rating on medication.
- SPID, TOPAR6, peak PID and peak PR were calculated.

Results:

- All active treatments were superior to placebo in pain measures ($P<0.05$).
- OX/APAP (10/650 mg) tended to be superior to OX-IR (15 mg) in the following measures. However, the statistical significance of the differences between them was not reported.
  - PI time-curve (Figure 1): OX/APAP was better than OX-IR
  - PR time curve (Figure 2): OX/APAP was better than OX-IR
  - SPID (Table II): 15.2±1.5 vs. 13.5±1.7
  - TOPAR6 (Table II): 18.5±0.8 vs. 15.4±1.5
  - Median time to onset (Table III): 32 min vs. 41 min (50 min on placebo)
  - Median duration of analgesia: 7.1 vs. 7.4 hrs (4.6 hr on placebo)

Comments

- Statistical significance of superior analgesia of OX/APAP combination over OX-IR was not reported; there was also limited data available in the article for further statistical analysis.
- The dose strength of OX between OX/APAP and OX-IR was different, 10 mg in OX/APAP vs. 15 mg in OX-IR, which showed a superior trend in the study. If the same OX dose strength was tested, OX/APAP would likely be statistically superior to OX-IR; however, in any scenario, without APAP-controlled arm, additional analgesic effects of the combination would be hardly assessed.
- The primary objective of this was to compared OX-CR and OX-IR (either alone or combination).

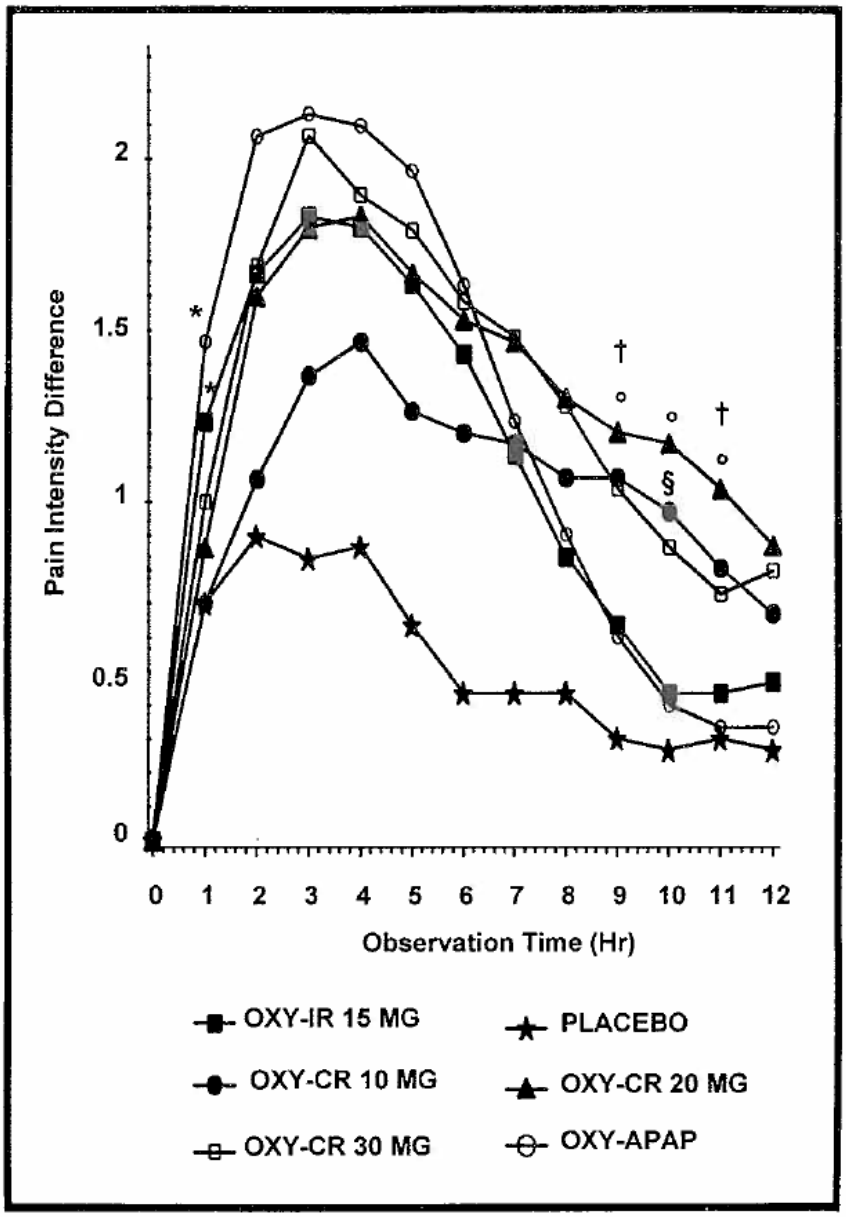


*Figure 1. Time–effect curves for mean pain intensity difference (PID) scores (categorical scale) plotted against time. * At 1 hour, 10 mg oxycodone plus 650 mg acetaminophen (APAP) and immediate-release (IR) oxycodone 15 mg were significantly better (P ≤ 0.05) than controlled-release (CR) oxycodone 20 and 30 mg. ○ At 9, 10, and 11 hours, CR oxycodone 20 mg was significantly better (P ≤ 0.05) than IR oxycodone 15 mg. † At 9 and 11 hours, CR oxycodone 20 mg was significantly better (P ≤ 0.05) than oxycodone plus APAP. § At 10 hours, CR oxycodone 30 mg was significantly better (P ≤ 0.05) than oxycodone plus APAP.*

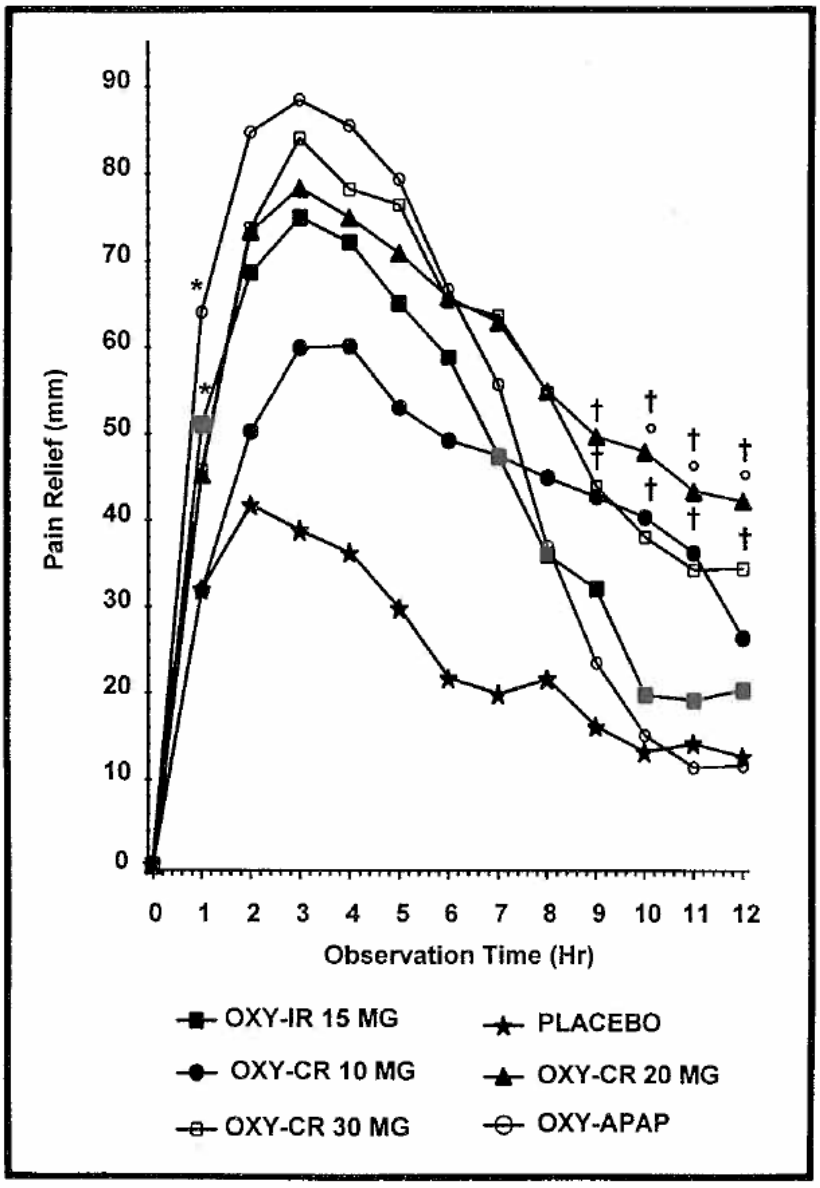


*Figure 2. Time–effect curves for mean pain relief scores (VAS) plotted against time. Categorical scale was similar to VAS. * At 1 hour, 10 mg oxycodone plus 650 mg acetaminophen (APAP) and immediate-release (IR) oxycodone 15 mg were significantly better (P ≤ 0.05) than controlled-release (CR) oxycodone 20 and 30 mg. ○ At 10, 11, and 12 hours, CR oxycodone 20 mg was significantly better (P ≤ 0.05) than IR oxycodone 15 mg. † At 9, 10, 11, and 12 hours, CR oxycodone 20 and 30 mg were significantly better (P ≤ 0.05) than oxycodone plus APAP.*

TABLE II

Measures of Analgesic Efficacy

Parameter*	Treatment Group					
	CR Oxycodone			IR Oxycodone (N = 30)	Oxycodone + APAP (N = 30)	Placebo (N = 30)
	10 mg (N = 30)	20 mg (N = 30)	30 mg (N = 30)			
SPID†	12.80 (1.98)‡	16.33 (2.01)‡	16.80 (1.87)‡	13.50 (1.69)‡	15.17 (1.47)‡	6.37 (1.48)
TOTPAR6†	11.67 (1.44)‡	15.60 (1.15)§	16.27 (1.22)§	15.43 (1.49)‡	18.53 (0.80)§	7.53 (1.24)
TOTPAR†	20.87 (2.86)‡	27.23 (2.81)‡	27.07 (2.67)‡	22.27 (2.55)‡	24.53 (1.76)‡	11.20 (2.35)
PPID†	1.70 (0.20)	2.20 (0.15)§	2.23 (0.16)§	2.10 (0.20)‡	2.50 (0.09)§	1.30 (0.21)
TPPID†	4.80 (0.73)	3.10 (0.37)§	3.00 (0.48)§	3.70 (0.65)‡	2.23 (0.21)§	5.73 (0.87)
PPAR†	2.67 (0.29)	3.50 (0.16)§	3.40 (0.19)§	3.20 (0.26)‡	3.83 (0.08)‖	2.10 (0.29)
TPPAR†	4.63 (0.72)	3.13 (0.36)‡	2.67 (0.37)§	3.70 (0.65)	2.27 (0.20)§	5.20 (0.82)
Overall pain relief†	2.40 (0.27)‡	3.17 (0.19)§	3.13 (0.21)§	2.90 (0.24)‡	3.37 (0.14)§	1.76 (0.27)
Global rating†	2.87 (0.24)	3.43 (0.23)‡	3.63 (0.23)	3.47 (0.25)‡	3.67 (0.16)§	2.17 (0.23)
REMED 12 hrs no. (%)	17 (56.6)¶	15 (50.0)¶	18 (60.0)	22 (73.3)	25 (83.3)	25 (83.3)
REMED 24 hrs no. (%)	23 (76.6)**	21 (70.0)††	25 (83.3)	28 (93.3)	29 (96.6)	27 (90.0)

* *Categorical scores (VAS were similar).*
† *Mean (standard error).*
‡ *Significantly different (P ≤ 0.05) from placebo.*
§ *Significantly different (P ≤ 0.05) from placebo and 10 mg CR oxycodone.*
‖ *Significantly different (P ≤ 0.05) from placebo, 10 mg CR oxycodone, and IR oxycodone.*
¶ *Significantly different (P ≤ 0.05) from placebo and Oxycodone + APAP.*
** *Significantly different (P ≤ 0.05) from Oxycodone + APAP.*
†† *Significantly different (P ≤ 0.05) from Oxycodone + APAP and IR oxycodone.*
CR, controlled-release; IR, immediate-release; APAP, acetaminophen; SPID, sum of pain intensity difference; TOTPAR6, total pain relief at 6 hours; TOTPAR, total pain relief at 12 hours; PPID, peak pain intensity difference; TPPID, time to PPID; PPAR, peak pain relief; TPPAR, time to PPAR; REMED 12 hrs, patients remedicating within 12 hours; REMED 24 hrs, patients remedicating within 24 hours.

TABLE III

Onset and Duration of Relief, Time to Remedication, and Number of Patients Remedicated During the 12-hour Study Period (for Patients with Subjective Onset of Relief)

	Patients with Onset No. (%)	Time to Onset by Percentile (min)			Duration of Relief by Percentile (hrs)			Time to Remedication by Percentile (hrs)			Patients Remedicated No. (%)
		25	50	75	25	50	75	25	50	75	
CR oxycodone											
10 mg	22 (73.3)	39.0	61.5*	102.0	5.6	12.0*	12.0	7.2	12.0†	12.0	8 (36.4)*
20 mg	28 (93.3)‡	30.0	58.0*	88.0	4.6	9.8*	12.0	6.3	12.0§	12.0	13 (46.4)§
30 mg	27 (90.0)‡	29.0	46.0‖	90.0	7.3	9.6*	12.0	8.2	11.4§	12.0	15 (55.6)§
IR Oxycodone	25 (83.3)‡	30.0	41.0	47.0	5.6	7.4	9.0	7.2	9.0	12.0	18 (72.0)
Oxycodone + APAP	30 (100.0)‡	26.0	32.0	46.0	5.0	7.1	8.4	6.4	8.1	10.0	25 (83.3)
Placebo	16 (53.3)	24.5	50.0	70.0	2.9	4.6	12.0	5.0	7.4	12.0	11 (68.7)

* *Significantly different (P ≤ 0.05) from Oxy-IR and Oxy APAP.*
† *Significantly different (P ≤ 0.05) from placebo, Oxy-IR, and Oxy-APAP.*
‡ *Significantly different (P ≤ 0.05) from placebo.*
§ *Significantly different (P ≤ 0.05) from Oxy-APAP.*
‖ *Significantly different (P ≤ 0.05) from Oxy-IR 15 mg.*
CR, controlled-release; IR, immediate-release; Oxycodone + APAP, immediate-release oxycodone (10 mg) plus acetaminophen (650 mg).

7-4. Codeine/APAP Combination: Full-factorial design study #1

Gertzbein SD et al: Analysis of the analgesic efficacy of acetaminophen 1000 mg, codeine phosphate 60 mg, and the combination of acetaminophen 1000 mg and codeine phosphate 60 mg in the relief of postoperative pain. ***Pharmacotherapy*** 6(3); 104-107, 1996 [13]

Design: randomized, double-blind, single dose in patients with pain due to post-surgery.

Subject and treatment: n=116 patients with at least moderate pain after orthopedic or general surgery (*types were not specified in the report)* were allocated to the following 3 treatment groups:

- APAP/Codeine (1000/60 mg), n=45
- APAP (1000 mg), n=45
- Codeine (60 mg): n=23

Pain Assessment:

- At 0.5, 1, 1.5, 2, 3, 4 and 5 hours post-dosing
- PI on 5-point scale and VAS; PR on 5-point scale, global rating on medication.
- PID, SPID, peak PID, TOPAR5, peak PR, at least half-pain gone

Results:

- Analgesic effects: codeine/APAP > APAP>codeine (Figures 1 and 2)
- Combination was statistically superior to codeine in SPID and TOTPAR, but not statistically superior to APAP

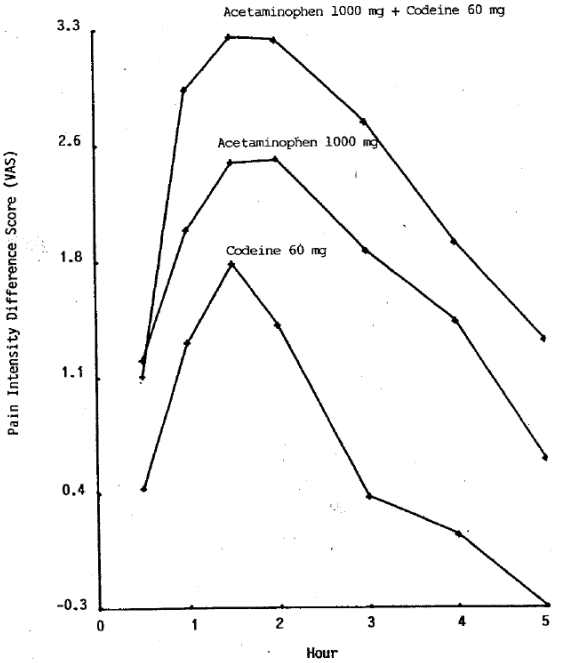


Figure 1. Mean pain intensity difference scores (VAS)

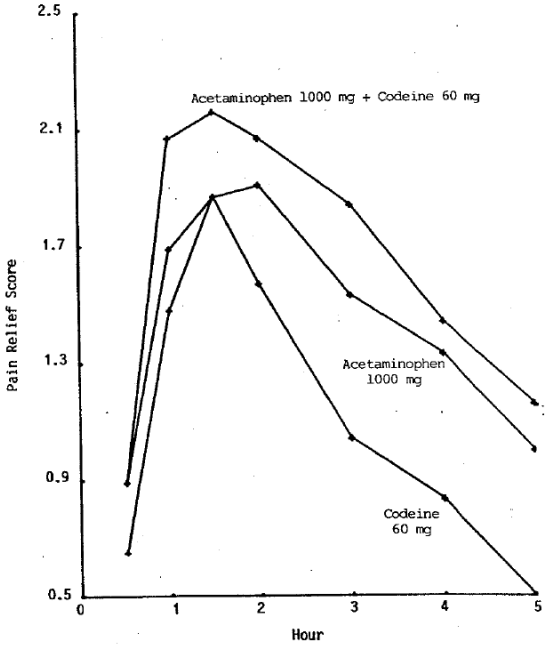


Figure 2. Mean pain relief scores versus time in hours.

7-5. Codeine/APAP Combination: Full-factorial design study #2

Quiding H and Hagguist S-O: Visual analogue scale and the analysis of analgesic action. ***Eur J CLin Pharmacol*** 24 (4): 475-478, 1983

Study design: randomized, double-blind, single-dose in acute pain

Subject and treatment: n=90 male patients with meniscectomy were randomized to 4 groups with the following single-dose treatments:

- Codeine/APAP (60/1000 mg) x2 tablets, n=25
- Codeine (60 mg) x2tablets, n=25
- APAP (1000 mg) x2 tablets, n=25
- Placebo, n=15

Pain assessment: 4 hours post dosing (0.5, 1, 2, 3, and 4 hours)

- PI on 100-mm VAS
- Time-weight total PI
- PID and % pain reduction (PR, % of PID)
- SPID
- Rescue medication

Statistical Analysis

- Parametric: one-way analysis of variance
- Non-parametric: Kruskall-Wallis method

Results

- Patient disposition and dropouts are shown in Table 1. A total of 24 patients (27%) were dropped out or excluded from the analysis; the final evaluable numbers of patients were: 16 on codeine/APAP, 20 on APAP, 18 on codeine and 10 on placebo.
- With parametric analysis (Table 2), codeine/APAP combination was statistically superior to codeine alone, but not to APAP alone, in PID.
- With non-parametric analysis (Table 3), codeine/APAP combination was statistically superior to codeine in PID and PR (% PID), to APAP in PR but not PID.
- Additional analgesics taken within 4 hours post dosing was 27% on Codeine/APAP combination, 77% on codeine alone, 45% on APAP alone and 58% on placebo. There was statistical significance between codeine/APAP and codeine.

Comments

- There were no statistical significance in the differences between active treatments and placebo.
- Codeine/APAP combination was statistically superior in analgesic effects to codeine but not to APAP.

- However, the study had the following limitations and flaws:
  - The sample size was too small, plus high dropout and exclusion (27%) during the study.
  - PID and PR (% PID) were not independent variables in this study and they should have the same statistical trend. However, the superiority of codeine/APAP over codeine or APAP was different in PID and PR in statistical significance.
  - Mean pain reduction in the codeine group was higher than in placebo the group (-36% vs. -9% in Table 2 and -26% vs. -13% in Table 3). However, there was one outlier in the codeine group who had an increase in pain intensity (PI) of 459%; this is reflected in the large standard deviation reported in Table 2.
  - More patients in the codeine group took rescue medication (77% vs. 58%).
  - SPID was planned but not reported.

Table 1. Details of the patients; m ± (SD)

Treatment		Age [years]	Weight [kg]	Duration of surgery [min]	Duration of bloodless field [min]	Removal of cartilage	End of operation – First postoperative tablet [h]
Paracetamol plus codeine	($n=22$)	33 (9.6)	83 (13.6)	39 (23.1)	57 (23.9)	9%	7.3 (2.6)
Paracetamol	($n=22$)	34 (12.8)	82 (9.8)	38 (19.7)	57 (21.2)	–	7.0 (2.8)
Codeine	($n=22$)	36 (10.7)	79 (11.5)	38 (15.7)	56 (15.7)	–	6.3 (2.1)
Placebo	($n=12$)	38 (11.3)	78 (10.0)	45 (25.5)	58 (25.8)	8%	6.9 (2.4)

Table 2. Initial painscore and different efficacy variables; m ± (SD)

Treatment	Initial pain score [mm]	Mean pain intensity [mm]	Mean pain intensity difference [mm]	Mean pain reduction
Paracetamol plus codeine ($n=16$)	56 (21.6)	44 (13.6)	12 (17.0)	12% (39.0)
Paracetamol ($n=20$)	57 (15.3)	53 (20.1)	5 (16.0)	3% (42.3)
Codeine ($n=18$)	52 (21.4)	57 (19.3)	- 6 (17.0)	- 36% (111.8)
Placebo ($n=10$)	49 (22.1)	51 (24.4)	- 1 (18.0)	- 9% (38)

Table 3. Initial pain score and different efficacy variables; median and quartiles (q_1, q_3)

Treatment	Initial pain score [mm]	Mean pain intensity [mm]	Mean pain intensity difference [mm]	Mean pain reduction
Paracetamol plus codeine ($n=16$)	56 (40, 72)	45 (35, 55)	12 (5, 24)	17% (9, 36)
Paracetamol ($n=20$)	54 (46, 71)	62 (38, 67)	3 (- 2, 7)	5% (- 6, 13)
Codeine ($n=18$)	50 (37, 62)	56 (43, 67)	0 (-14, 3)	0% (-26, 5)
Placebo ($n=10$)	44 (35, 64)	48 (32, 62)	- 5 (-15, 18)	-13% (-38, 33)

7-6. Codeine/APAP Combination: A meta-analysis on efficacy trials (combination *vs.* APAP or placebo)

Moore A et al: Paracetamol with and without codeine in acute pain: a quantitative systematic review. Pain 70: 193-201, 1997 [14]

Data collection: The following randomized controlled trials (RCTs) of APAP in post-operative pain (post-dental extraction, post-surgical or postpartum pain) were identified from multiple databases and included in this meta-analysis:

- 31 RCTs: APAP ***vs.*** placebo with n=2515 patients
- 19 RCTs: APAP/codeine ***vs.*** placebo with n=1204 patients
- 13 RCTs: placebo/codeine ***vs.*** APAP (the same dose) with n=874 patients

Dada process and analysis

- Analgesic outcomes from each RCT were converted to % maximum TOTPAR (%maxTOTPAR):
  - %maxTOTPAR = mean TOTPAR/calculated maximum TOTPAR
  - Proportion of patients with > 50% maxTOTPAR = 1.33xmean %maxTOTPAR – 11.5
- The >50% maxTOTPAR was used to calculate relative risk (RR)and number-needed-to-treated (NNT):
  - NNT= Proportion with >50%maxTOTOPAR x total number of patients in the treatment group
  - RR was calculated with 95% CI suing random effects model.
- Relative efficacy:
  - Direct comparisons: on NNT
  - Indirect comparisons: difference from placebo among different treatment groups

Results:

- Addition of codeine 60 mg to APAP produces additional pain relief. The difference was about 12% between APAP/codeine and APAP alone (Fig 1 and Table 2).
- Comparison between APAP/codeine and codeine was not reported in this article, but the authors compiled codeine data across other studies without specifying the data source, as shown in Fig 2.

Comments:

- The analysis suggests that addition of codeine to APAP increased analgesia in acute pain treated with single dose.
- No current comparison with codeine alone
- It is unknown if % maxTOTPAR calculation and the descriptor of effectiveness using NNT was appropriately validated. The author did not provide detailed rationale for this method but just referred to their previous publications.
- The pooled sample size was too small

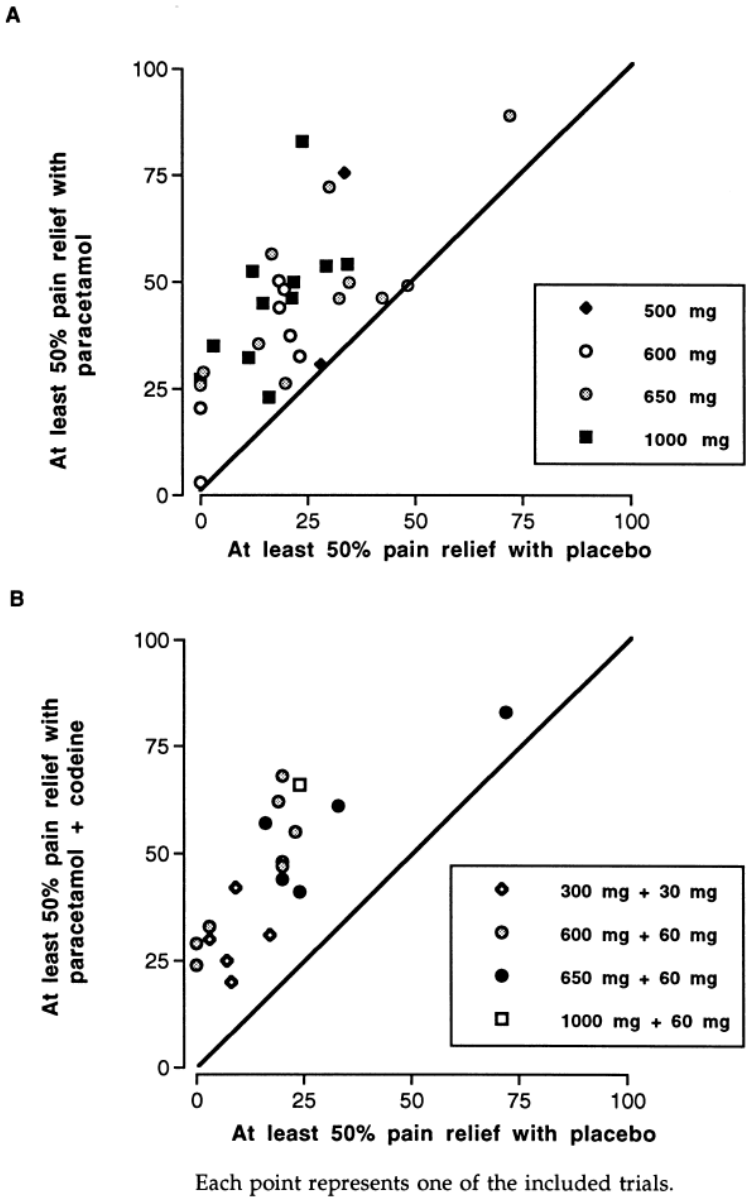


Fig. 1. Plot of single dose studies of paracetamol (A) or paracetamol plus codeine (B) against placebo in postoperative pain.

Table 2

Summary risk ratios and number-needed-to-treat for trials of paracetamol and codeine against placebo and against paracetamol alone

Number of trials	Drug dose (mg) paracetamol + codeine	>50%maxTOTPAR on paracetamol plus codeine	>50%maxTOTPAR on placebo	Risk ratio (95% CI)	NNT (95% CI)
Paracetamol plus codeine versus placebo					
5	300 + 30	69/246	17/196	3.0 (1.8–5.0)	5.3 (3.8–8.0)
13	600/650 + 60	219/415	88/432	2.6 (2.1–3.2)	3.1 (2.6–3.8)
1	1000 + 60	27/41	4/17	2.8 (1.2–6.8)	2.4 (1.5–5.7)
Paracetamol plus codeine versus same dose of paracetamol alone					
11	600/650 + 60	180/349	148/353	1.19 (0.98–1.44)	10 (5.9–43)
2	1000 + 60	57/86	44/86	1.27 (1.08–1.48)	6.7 (3.4–174)
13	All doses + 60	237/435	192/439	1.20 (1.02–1.40)	9.1 (5.8–24)

Doses of paracetamol are given first. All data sets were homogeneous. Studies were predominantly in oral surgery (14 trials for paracetamol plus codeine against placebo and 10 trials for paracetamol plus codeine against paracetamol alone).

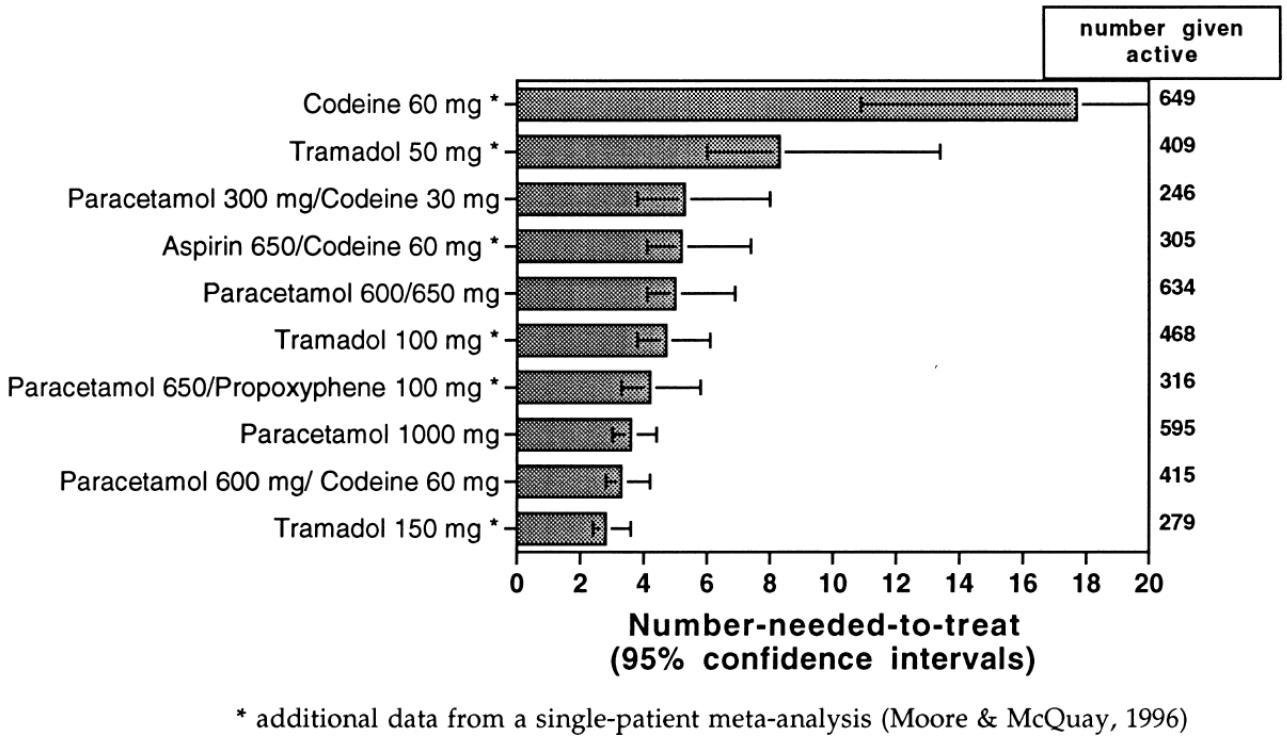


Fig. 2. NNT for at least 50% pain relief for single oral doses of analgesics in moderate or severe postoperative pain compared with placebo.

The addition data (with *) were presented as Abstract in *VIII*^{the} *World Congress on Pain* (1996). The detailed data source and analyses are not discussed in this article.

7-7. Oxycodone/APAP Combination: A partial-factorial design study; chronic pain

Caldwell JR et al: Treatment of osteoarthritis pain with controlled release oxycodone or fixed combination oxycodone plus acetaminophen added to nonsteroidal antiinflammatory drugs: a double blind, randomized, multicenter, placebo controlled trial. ***J Rheumatol*** 26: 862-9, 1999

Study Design: randomized, double-blind, placebo-controlled trial.

Study subjects:

- N=167 adult patients (mean age: 58 yrs, 68% female) with moderate to severe OA pain despite regular use of NSAID (all patients continued NSAID therapy at stable pre-study dosage throughout the study)
- N= 107 of 167 were qualified for randomization after the 30-day open-label treatment with Oxycodone IR

Treatment:

Open-label titration (30 days, n=167):
Oxycodone IR 5 mg, qid (20-60 mg/day) until PI < moderate and tolerable; no washout period prior to the double-blind phase.

Double-blind treatment (30 days, n=107)

- Oxycodone CR (OxyContin tablets, 10 mg): bid (8 AM and 8 PM); n=34
- Oxycodone/APAP (5/325 mg): qid; n=37
- Placebo; n=36

Efficacy assessment:

- Patient global assessment
- Pain intensity (4-point categorical scale)
- Global quality of sleep (5-point categorical scale)

Results

Dropouts: 34% (n=36/107)

- Placebo: 18/36 (13 LOE, 3 AE)
- Oxycodone CR: 7/34 (3 AE and 3 LOE)
- Oxy/APAP: 11/37 (5 AE and 4 LOE)

LOCF imputation for missing data from the dropouts, and the ITT population was used for primary efficacy analysis.

Efficacy:

- Titration with oxycodone IR:
  - Mean PI (0 = none to 3 = severe) decreased from 2.44 ±0.04 to 1.38 ±0.05 (p = 0.0001)

  - Quality of sleep (1 = very poor; 5 = excellent) improved from 2.58 ±0.08 to 3.57 ±0.07 ($p = 0.0001$).
  - Mean dose of oxycodone IR was about 40 mg/day.

- Double-blind phase (after 2 and 4 weeks):
  - Pain intensity and quality of sleep were significantly improved in both active groups compared with the placebo group ($p \leq 0.05$) during the double blind trial.
  - Pain intensity and sleep scores were comparable in (no significant difference between) both active groups during double blind treatment.

Safety:
Typical opioid AEs: somnolence, constipation, nausea, pruritus, dizziness, dry mouth and vomiting

Nausea ($p=0.03$) and dry mouth ($p=0.09$) were less common with controlled release oxycodone than immediate release oxycodone-APAP.

Conclusion:

- Oxycodone CR q12h and oxycodone-APAP IR qid, added to NSAID, were superior to placebo for reducing OA pain and improving quality of sleep.

- The active treatments (Oxy CR and Oxy/APAP) provided comparable pain control and sleep quality (no statistical difference). From compliance standpoint, less frequent dosing schedule of Oxy CR may improve compliance, particularly for around-the-clock pain control.

- Oxy CR showed less opioid AEs than Oxy/APAP: similar profile but with a trend to fewer AEs in Oxy CR.

Comments:

- Chronic pain trial (30 days) in OA patients. There was comparable analgesia between Oxy CR bid and Oxy/APAP (IR qid), suggesting that Oxy CR would improve compliance for around-the-clock pain control as compared to Oxy/APAP.

- This was an add-on trial, all subjects continued previous NSAID therapy, but the detailed information about NSAID used during the study was not reported.

- There was no washout period after the 30-day open-label titration with oxycodone IR; rationale not reported.

Appendix 8. Literature Summary Table of Efficacy Studies on Hydrocodone/APAP Combination Products

Study Medication	Study Indication	Study Subject	Study Design	Efficacy	Safety	Publication
HC/APAP (10/1000mg), HC (10mg), APAP (1000mg), Codeine (60mg), Placebo	Acute pain, (postpartum)	N=108 patients (n=22/arm)	R/DB/PC single-dose, 6-hr pain assessment (hourly)	All Txs were superior in analgesia (PR, PI and 50%-responder) to placebo; HC/APAP > HC or APAP but only 50%-responder showed additive analgesia		Beaver 1980[8] ***Detailed review in Appendix 1-1***
HC/APAP (7.5/500mg) OX/APAP (5/325mg) OX/IB (5/400mg) placebo	Acute pain, (post-op dental pain); Single-dose	Total n=249 patients (62/arm)	R/DB/PC single-dose, 6-hr pain assessment (hourly)	Dropout rates (w/ LOCF): 18% (OX/IB), 49% (OX/APAP), 74% (HC/APAP) and 73% (PC) TOTPAR6 and SPID6: OX/IB>OX/APAP=HC/APAP>PC ($p<0.01$) Rescue medication (% pt) PC>HC/APAP>OX/APAP>OX/IB Time to rescue (short to long): OX/IB<OX/APAP=HC/APAP<placebo	Common AEs: nausea and vomiting; OX/APAP>HC/APAP>OX/IB >PC	Litkowski LJ et al, 2005[44]
HC/APAP (7.5/750mg), Ketorolac (10mg), Placebo (6 hour then keto)	Acute pain, Ambulatory arthroscopic or laparoscopic tubal ligation; Single-dose & multiple-dose (q4-6h)	Total n=252 patients (82-87/arm)	R/DB, Assessment at single-dose phase (hourly x6 hrs) and at multiple-dose phase (daily x3 days)	Overall dropout rate: 70% (63 HC/AP, 70% keto, 77% PC) at 6-hr and 78% at day 3 6-hour analgesia in arthroscopy: HC/APAP < ketorolac < placebo 6-hour analgesia in laparoscopic tubul ligation: no difference among 3 txs At end of days 1,2,3 no differences in analgesia among 3 txs.	Common AEs: nausea, vomiting and somnolence; HC/APAP>Ketorolac	White et al, 1997[45]
HC/APAP (7.5/750mg, q4-6h) Rofecoxib (50mg, qd) for 5 days	Acute pain, Functional endoscopic sinus surgery (FESS)	N=28 adult patients. 14/arm (from 40 enrolled)	R/DB	30% dropout rate Only assessed the mean peak pain score at each day for 4 days:	No differences in the common AEs: headache, drowsiness, constipation, sleep problem, nausea/vomiting	Church et al: 2006[25]
HC/APAP (5/325mg) OX/APAP (5/325mg)	Acute pain, Fracture with pain ≥5 on 0-10	N=73 patients from ER; 34 HC/APAP	R/DB single-dose	No dropouts; Pain score at 30 and 60 min post dosing: OX/APAP slightly better than HC/APAP (but no	Similar between 2 txs in common AEs: nausea,	Marco et al: 2005[46]

Study Medication	Study Indication	Study Subject	Study Design	Efficacy	Safety	Publication
	scale	and 39 OX/APAP		stat significance)	vomiting, itching, drowsiness; but HC/APAP had higher % constipation.	
HC/APAP (7.5/650mg) Tramadol/APAP (75/650mg) placebo Single dose first 4 hr, then qid x5 days	Ankle sprain with partial ligament tear VAS≥50 mm (100-mm scale); NRS 2-3 (4-point)	N=204 HC/APAP N=192 Tramadol/APAP	R/DB/PC single- and multiple-dose	Dropout rate: 13% (due to AE and LOE); Analgesia at the first 4 hours: HC/APAP & Tram/APAP > placebo (P<0.05); no difference between HC/APAP and Tram/APAP For days 1-5: mean PR HC/APAP=Tram/APAP>Placebo, but no difference in mean PI and final PR/PI among 3 groups	Comparable between HC and Tram in common AEs: somnolence, nausea, vomiting, dizziness,	Hewitt et al: 2006[24]
HC/APAP (10/650mg) Tramadol/APAP (37.5/325mg) Tramadol/APAP (75/650mg) placebo	Post-OP dental pain VAS≥50mm	N=200 patients; 50/arm	R/DB/PC/AC single-dose, 8-hr pain assessment	7.5% dropouts (with LOCF) Analgesia 0-8 hours post dosing: HC/APAP & Tram/APAP (75/650mg) > placebo (P<0.05) and HC slightly > Tram (but NS).	Common AEs: dizziness, nausea, vomiting, headache; HC>Tram	Fricke et al: 2002[47]
HC/APAP (10/1000mg) Celecoxib 200mg Placebo Single-dose (8hr), Multiple dose (tid x5 days)	Orthopedic surgery Bunionectomy, ligament reparie, open reduction and internal fixation of fracture, laminectomy or osoteotomy VAS≥45mm	N=418 136-141/arm	R/DB/PC/AC single- and multiple-dose, placebo pts re-randomized to either tx for multiple-dose period	All treatments superior to placebo in PID during first 6-hour assessment; During the 5-day multiple dose, celecoxib superior to HC/APAP	Overall common AEs: celecoxib was better than HC/APAP	Gimbel et al: 2000[48]
HC/APAP (10/1000 mg), Ketorolac (10 mg)	Post-op dental pain	N=207 pts with moderate pain	R/DB/PC in acute pain, single dose, 6-hour pain assessment	Both active treatments were superior to placebo in SPID3 and SPID6, TOTPAR3 and TOTPAR 6; Ketorolac was superior to HC/APAP	Higher frequency in HC/APAP combination	Fricke at al 1993 [49]

Study Medication	Study Indication	Study Subject	Study Design	Efficacy	Safety	Publication
placebo		post dental procedure (65-68/arm)	(PI on 4-point and 100-mmVAS, PR on 5-point)	combination		
HC/APAP (7.5/500 mg), Codeine/APAP (30/300 mg) placebo	Post-op dental pain	N=232 pts with moderate or severe pain post dental surgery	R/DB/PC single dose in acute pain, 6-hour pain assessment	Both treatments was superior to placebo, HC/APAP was superior to codeine/APAP	Typical opioid AEs	Forbes et al 1994 [50]

HC: hydrocodone (IR); APAP: acetaminophen; OX: oxycodone (IR); IB: ibuprofen (IR); PC: placebo control; NS: not statistical significance
R: randomized, DB: double-blind, PC: placebo-controlled,

Appendix 9. Literature Summary Table of Efficacy Studies on Oxycodone/APAP Combination Products

Study Medication	Study design Indication	Subjects	Efficacy Results	Safety Results	Publication
APAP/OX (500/5, 1000/5, 1000/10 mg), APAP (500 mg), OX (5 mg), Placebo; Single-dose	Randomized, placebo, ***full factorial*** in acute pain	N=298 pts with post-op dental pain	All active tx were superior to placebo; APAP/OX (500/5 mg) was superior to APAP (500 mg) alone or OX (5 mg) alone in PI time-course, PR time-course, SPID, TOTPAR, peak PR (but unknown statistical significance)	Typical OX AEs and the incidence related to OX dose (5 vs. 10 mg) No lab test (thus no LFT) for APAP	Cooper et al, 1980 [9] ***Detailed review in Appendix #1-2***
APAP/OX (650/10 mg), ***OX-IR (15 mg),*** OX-CR (10, 20, 30 mg), Placebo Single-dose	R/DB/PC single-dose in acute pain; 12-hour pain assessment: PI on 4-point scale, PR on 5-point scale and VAS, overall PR at 12 hr and global rating	N=180 pts with post Abdominal or Gyn surgical pain, 30/arm of 6 arms	Combo was comparable to OX-CR (30 mg) and OX-IR (15 mg) Onset: OX/APAP shorter than OX-IR and OX-CR (30 mg) Duration: OX/APAP and OX-IR=7 hr and OX-CR 10-12hr	Typical AEs. Comparable incidence among active tx groups. No lab test was conducted.	Sunshine et al, 1996 [10] ***Detailed review in Appendix #1-3***
APAP/OX (325/10mg), OX-CR (20 mg), Placebo Single-dose	R/DB/PC, single-dose in acute pain; 6-hour pain assessment: PR on 5-point scale and VAS; PI on 4-point scale and VAS, 2-stopwatch	N=150 pts with post-op dental pain (VAS≥50 mm); N=59 (OX), 61 (OX-CR) and 30 (PC)	Both treatment s were statistically superior to placebo in all pain measures; OX/APAP was statistically superior to OX-CR in peak PID, peak PAR, SPID and SPRID, onset, and use of rescue medication; OX/APAP > OX-CR in TOPAR6 but not statistical	Common AEs consistent with opioid class; less AE incidence with OX/APAP than OX-CR; Had lab test but did not report LFT	Gammaitoni et al, 2003 [51]
APAP/OX (325/5 mg) qid, OX-CR (10 mg) bid, Placebo For 30 days	R/DB/PC in chronic pain (OA), PI and global sleep quality at week 2 and 4	N=107 OA pts pain < moderate after 30-day OL tx with 5 mg OX-IR; 34-37/arm	Dropout rate: 34% Both active txs were superior to placebo; comparable in pain control and sleep quality.	Opioid class AE; less incidence with OX-CR than OX/APAP	Caldwell et al, 1999 [30]
APAP/OX (650/10 mg), ***APAP (650 mg),*** Ketoprofen (50, 100mg),	R/DB in acute pain, single dose and multiple dose	N=240 pts with post C-section severe pain,	Single-dose: All active treatments except APAP were superior to placebo in PI and PR measures. No difference between APAP (650	Reported from only multiple-dose period. More AE incidence on	Sunshine et al, 1993 [52]

Study Medication	Study design Indication	Subjects	Efficacy Results	Safety Results	Publication
Placebo;	(q4hr x7days), PI on 4-point, PR on 5-point scales and global on 5-point hourly for 8 hours (single dose) and twice a day for multiple-dose	n=48 each of 5 arms	mg) and placebo; combination was superior to APAP for SPID, TOTPAR, time to peak, peak PID, pt global. Multiple-dose: comparable in PI, global and sleep quality among keto and APAP/OX (subjects in APAP alone and placebo arms were re-randomized to keto or APAP/OX during the multiple dose period)	OX/APAP combination (typical opioid AEs) than keto	

OX: oxycodone, OX-CR: oxycodone controlled release, OX-IR: oxycodone immediate release,
R: randomized, DB: double-blind, PC: placebo-controlled, OL: open-label, AC: active-controlled
PID: pain intensity difference, PR or PAR: pain relief
LFT: liver function test (such as ALT, AST, bilirubin)

Appendix 10. Literature Summary Table of Efficacy Studiers on Codeine/APAP Combination Products

Study Medication	Study design Indication	Subjects	Efficacy Results	Safety Results	Publication
APAP/Codeine (1000/60 mg), APAP (1000 mg), Codeine (60 mg)	R/DB single-dose in acute pain, 5-hour pain assessment	N=116 pts with ≥ moderate pain post orthopedic or general surgery, n=45/45/23	Combination was statistically superior to codeine alone in SPID, TOPAR, pain half gone and time to remedication; and non-statistically superior to APAP in all efficacy measures	No differences in AE among 3 tx groups.	Gertzbein et al, 1986 [13] ***Detailed review in Appendix 1-4***
APAP/codeine (1000/60 mg), APAP (1000 mg), Codeine (60 mg), Placebo	R/DB/PC single-dose in acute pain, 4-hour pain assessment (PI on VAS)	N=90 pts with pain post-surgery	APAP/codeine combination was superior in analgesic effects to either component (APAP or codeine alone), but statistical significance with codeine only.	No special	Quiding et al 1983 [12] ***Detailed review in Appendix 1-5***
APAP/Codeine (600/60, 650/60, 1000/60 mg), APAP (600, 650, 1000 mg)	Meta-analysis on 13 RCT: 10 in oral surgery; 3 in post-surgical pain	N=874 patients (unclear allocation per treatment)	Based on the number-needed-to-treated (NNT, for ≥ 50% PR), adding codeine 60 mg to APAP showed additional PR as compared to APAP alone (12% differences)	Not discussed	Moore et al 1997 [14] A meta-analysis; ***Detailed review in Appendix 1-6***
APAP/codeine (800/60 mg), APAP (1000 mg), Placebo	R/DB/PC single dose in acute pain 6-hpur pain assessment (PID, SPIS, TOTPAR, rescue med, global)	N= 125 pts with C-section; n=50 on combo or APAP, n=25 on placebo	Both active txs were statistically superior to placebo only in patients with server baseline pain (VAS>60mm) but not moderate baseline pain (VAS=40-60mm); APAP/codeine (800/60 mg) combination was superior to APAP (1000 mg) in severe baseline pain but not moderate baseline pain	No special	Bjune et al 1996[15]
APAP/Codeine (600/60mg) q-6hr, Codeine-CR (100, 200, 300 mg) q-12hr for 4 days	R/DB/AC in cancer pain, PI and PR hourly at days 1 and 4	N=24 pts with cancer pain	Codeine-CR 150 mg was equianalgesia to the APAP/codeine (600/60 mg); it was estimated that 90 mg from APAP/codeine q12hr equivalent to 150 mg codeine-CR, suggesting contribution of APAP to the analgesia	Opioid class AEs; AE incidence of APAP/codeine q6hr was between codeine-CR 100 mg and 200 mg q12hr	Chary et al, 1994 [48]
APAP/Codeine (9.6/1 mg/kg)	R/DB in acute pain, daily Wong-	N=51 children (3-12 yo) with	Comparable (no statistical difference) in time-course for pain level rated by children	APAP/codeine tended to increase AEs and	Moir et al, 2000[53]

Study Medication	Study design Indication	Subjects	Efficacy Results	Safety Results	Publication
APAP (15 mg/kg) For 10 days	Baker FACES pain rating for 10 days	tonsillectomy or adenoidectomy	or parents between APAP/codeine and APAP	decreased post-surgical oral normal diet vs. APAP alone	
APAP/Codeine (1000/30 mg), APAP (1000 mg)	R/DB/3-dose in acute pain, PI measured hourly for 12 hours	N=82 pts with post operative dental pain	APAP/codeine (1000/30 mg) was statistically superior to APAP (1000 mg) over 12 hours (in PI and rescue medication)	Comparable AE profile between 2 treatment groups	Macleod et al, 2002 [54]
APAP/codeine (1000/60 mg), APAP (1000 mg), APAP (2000 mg), Placebo	R/DB single-dose in acute pain, 6-hour pain assessment	N= 139 pts with post-op dental pain N=32-37 each of 4 arms	All active txs were statistically superior to placebo, combination was statistically superior to APAP 1000 mg and 2000 mg, APAP 2000 mg was non-statistically superior to APAP 100 mg	Not special	Skoglund et al 1991[55]
APAP/codeine (600/60 mg), APAP (600 mg) Ibuprofen (400 mh), Ketorolac (10 or 20 mg), placebo	R/DB single-dose in acute pain, 6-hour pain assessment	N=260 pts with postoperative dental pain, N=31-38 each of 6 arms	All active txs were statistically superior to placebo. Keto>Ibu>APAP and APAP/codeine; no statistically significant differences in the 6-hour analgesic effects among active tx groups; no statistical differences between APAP/codeine and APAP	Not special	Forbes et al 1990[56]
APAP/Codeine (1000/60 mg) APAP/Diclofenac (1000/100mg), APAP/Diclofenec/Codeine (1000/100/60mg), Diclofenac (100mg), APAP (1000mg)	R/DB in acute pain, single dose, 8-hour pain assessment (PI and PR)	N=120 pts with po-dental pain	APAP/Codeine was superior to APAP alone; APAP/Diclofenac was the best in pain relief;	Addition of codeine increased incidence of AEs.	Breivik et al, 1999 [57]
Codeine/APAP (30/500 mg), tid Placebo 7 days	R/DB in chronic pain, 7-day assessment: VAS, disability score, global	N=40 RA with ≥ moderate pain N=20/arm	2 dropouts in placebo (LOE), Codeine/APAP superior to placebo in 7-day SPID and in VAS score at days 4-7; in disability score at days 4-7.	Opioid class AEs.	Boureau et al 1991[31]
Codeine/APAP (30/500 mg) tid plus diclof (50 mg) qd;	R/DB in chronic pain, 7-day pain assessment	N=60 RA N=30/arm	Codeine/APAP (tid) and diclof (50 mg qd) was comparable in PI, global and stiffness/awakenings to diclof (50 mg bid)	Not special	Glowinski et al 1999[58]

Study Medication	Study design Indication	Subjects	Efficacy Results	Safety Results	Publication
Diclof (50 mg) bid 7 days					
Codeine/APAP (30/500 mg); Tramadol (50 mg) 2 capsules q8-hr x7 days	R/DB/cross-over (w/o washout) 7-day assessment	N=55 refractory chronic back pain	Comparable in pain relief		Muller et al 1998[33]

OX: oxycodone, OX-CR: oxycodone controlled release, OX-IR: oxycodone immediate release; R: randomized, DB: double-blind, PC: placebo-controlled, OL: open-label, AC: active-controlled; PID: pain intensity difference, SPID: sum of PID, PR or PAR: pain relief; LFT: liver function test (such as ALT, AST, bilirubin)

Appendix 11. Hepatotoxicity Studies on Opioid/APAP Combination in Healthy Adult Subjects (IND 55,965)

Study HXA1017. Randomized, double-blind, placebo-controlled study on hydrocodone/naltrexone/APAP combination (HXA) in healthy subjects to assess liver toxicity

[Preliminary summary of final liver function test results was submitted on December 16, 2003; the final study report has not been received. The IND was inactivated in April 2004.]

Study population: healthy adult subjects in 3 study sites were randomized to 4 treatment arms, n=28-29/arm

Treatment: double-dummy, q6-hr for 14 days, for a total of 56 doses.

- HXA (hydrocodone/naltrexone/APAP: 5/0.125/500 mg): 2 tablets
- Vicodin (hydrocodone/APAP: 5/500mg): 2 tablets
- Vicodin+Naltrexone: 2 tablets Vicodin plus 2 tablets of Naltrexone (0.125 mg)
- Placebo: 4 tablets

Liver function test: blood samples were colleted in the following schedule for ALT and AST tests:

- Screening: < 30 days prior to dosing
- Baseline: 24 hours prior to dosing
- Day 1: just prior to start of dosing
- Days 2, 4, 6, 8, 10, 12, 15: just prior to end of dosing
- Day 17: 3 days post dosing

Results

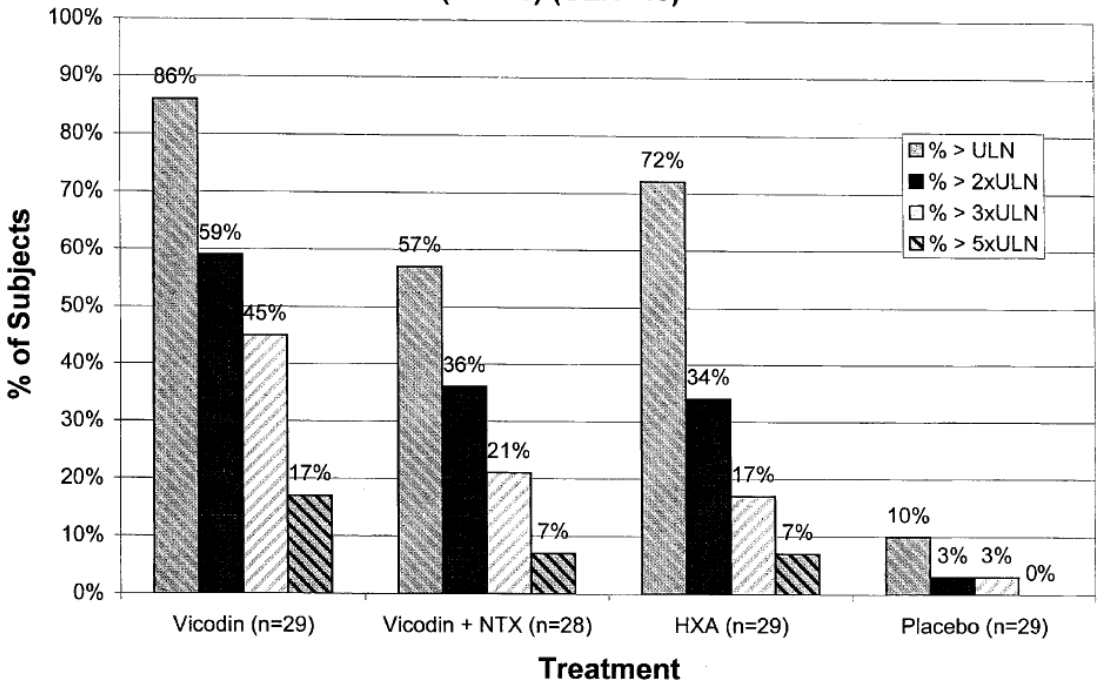
ALT:

- More subjects in each of active treatment group with elevated ALT than those in placebo (Figure 1)
- ALT >5xULN: 9 subjects (2 on HXA, 5 on Vicodin, 2 on VX) during or after dosing
- One subject: 11 x ULN (or 37 x baseline)
- Elevated ALT resolved within approximately 2 weeks after dosing was stopped.

AST: parallel ALT but with smaller magnitude

Bilirubin: No significant elevations at any time.

Figure 1: HXA1017 Central Laboratory Data
Incidence (%) of ALT Elevations by Treatment
(n=115) (ULN=40)



Study HXA1007: Randomized, cross-over, multiple-dose PK study on hydrocodone/naltrexone/acetaminophen (HXA) combination tablets in healthy subjects under fasted condition

Study subjects: n=13 healthy, MF, 18-45 years of age

Treatment: hydrocodone/naltrexone/acetaminophen (5/0.125/500 mg)

- Period #1: 1 tablet q6h x 13 doses (72 hours)
- Period #2: 2 tablets q6h x 13 doses (72 hours)

Washout interval: 5 days (switched on day 8)

Assessment:

- PK: routine parameters and analyses
- Safety: clinical lab included LFT (ALT, AST and bilirubin)

Results:

- The time-course of mean values of ALT and AST from each subject is shown in the Figures 7 and 8 (adapted from the sponsor's report).
- Elevated ALT >ULN: 62% (8/13) subjects with 15% (2/13) >2xULN
  1 tablet HXA: 33% and 2 tablets: 71%
- Elevated AST >ULN: 46% (6/13) subjects
  1 tablet HXA: 17% and 2 tablets HXA: 57%

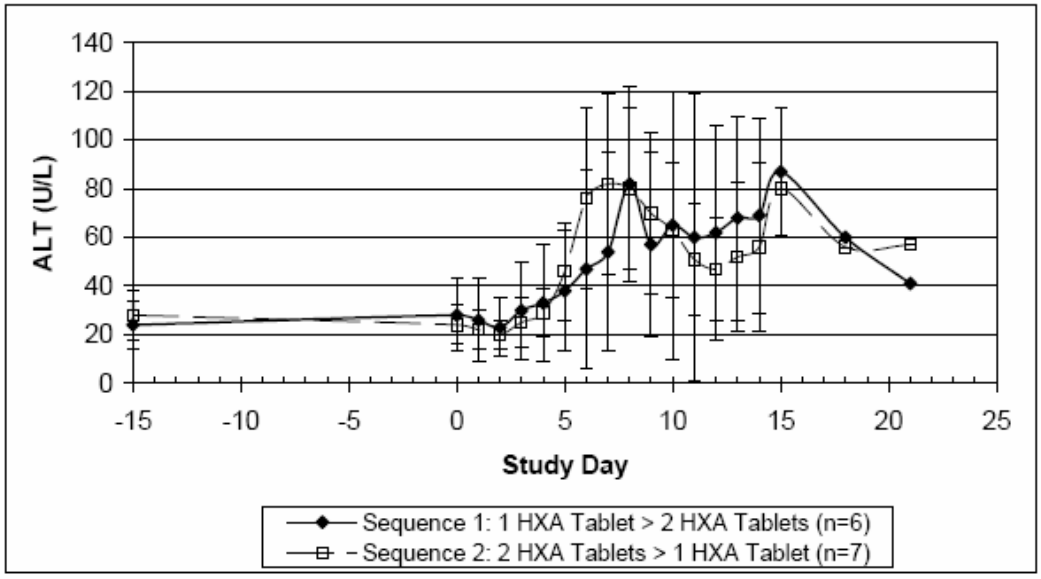


Figure 8. Mean (±SD) ALT Values by Treatment Over Time:

Safety Population (N = 13)
Note: Period 1 = Day 1 to Day 7 (Day 1 to Day 4 with dosing), Period 2 = Day 8 to Day 14 (Day 8 to Day 11 with dosing). Not all subjects had LFT data for 21 days. Those subjects with elevated LFTs at the end of the study (Day 14) had repeat LFTs until their levels returned to within normal limits (Days 15-21).
Cross references: Figure 14.4.3.2, Table 14.3.6.1, and Appendix 16.2.8.2.

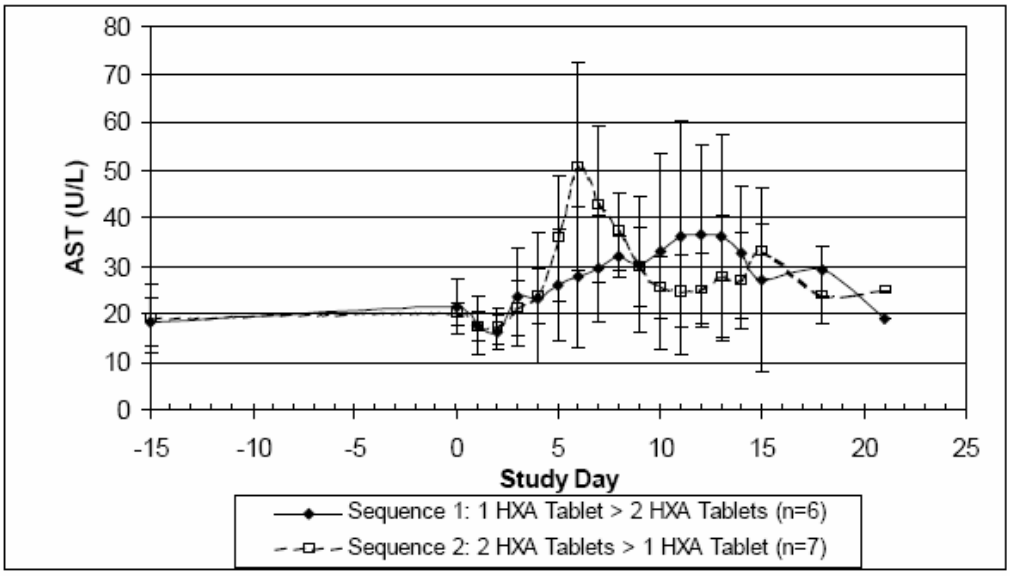


Figure 7. Mean (±SD) AST Values by Treatment Over Time:

Safety Population (N = 13)
Note: Period 1 = Day 1 to Day 7 (Day 1 to Day 4 with dosing), Period 2 = Day 8 to Day 14 (Day 8 to Day 11 with dosing). Not all subjects had LFT data for 21 days. Those subjects with elevated LFTs at the end of the study (Day 14) had repeat LFTs until their levels returned to within normal limits (Days 15-21).
Cross references: Figure 14.4.3.1, Table 14.3.6.1, and Appendix 16.2.8.2.

Appendix 12. Report from the Acute Liver Failure Study Group

Larson AM et al: Acetaminophen-Induced Acute Liver Failure: Results of a United States Multicenter, Prospective Study. ***Hepatology*** 42: 1364-1372, 2005[41]

Study Design: Historical prospective evaluation of demographic, clinical, laboratory and outcome information all subjects meeting entry criteria for acute liver failure (ALF) at the 22 academic centers participating in the ALF Study Group in US between Jan 1, 1998 and Dec 31, 2003 (6 calendar years).

ALF entry criteria:

- INR≥1.5
- Hepatic encephalopathy
- Within 26 weeks of illness onset without apparent chronic liver disease
- Informed consent from patients' legal next of kin (because of encephalopathy)
- Outcomes defined as liver transplantation, discharge or 3 weeks after admission

APAP exposure information for each patient

- Total dose
- Type of APAP product
- Duration of use

Criteria for causality between APAP and ALF:

- A history of potentially toxic acetaminophen ingestion (*i.e.*> 4 g/day, the maximum dose recommended on the package) within 7 days of presentation;
- Detection of any level of acetaminophen in the serum; OR
- A serum ALT > 1,000 IU/L with a history of acetaminophen ingestion, irrespective of the acetaminophen level
- Exclusion:
    - acute hepatitis A and B
    - hepatic ischemia
    - autoimmune hepatitis
    - Wilson disease

Confirmatory diagnosis:

- Case report forms reviewed by investigator at the central site (UTSW)
- Annual on-site audits conducted by the central site

ALF severity assessment:

- The Acute Physiology and Chronic Health Evaluation (APACHE) II score
- Model for End Stage Liver Disease (MELD) score
- The King's College Hospital criteria for ALF ("King's Criteria")

Definitions:

- Intentional (suicidal) ingestion: a single time-point ingestion in a patient admitting suicidal intent
- Unintentional ingestion: a multiple-time-point ingestion to relieve pain or other somatic symptoms with denial of suicidal intent.
- Alcohol abuse: was defined as consumption of ≥40 g alcohol per day in men and ≥20 g alcohol per day in women.

Results

Overall study population

- A total of 662 ALF cases (all causes) enrolled during the 6-year from the 22 centers, 302 cases (46% of 662) were APAP-related hepatotoxicity with the following 17 exclusions:
  - 10 of them with insufficient data
  - 17 with competing causes: viral hepatitis, concomitant polydrug use or shock
- The 275 APAP-related ALF cases (42% of 662) for final evaluation (Table 1),
  - APAP-related ALF increased from 28% in 1998 to 51% in 2003 (Figure 1).
  - >80% of the patients were transferred from other institutions with significant encephalopathy (so compromising history taking)
  - The 22 participating centers represented approximately 30% of US transplant capability
  - An additional 40% of cases were not enrolled because of lack of informed consent or inadequate information to ensure the diagnosis
  - Estimated total APAP-related ALF cases at US transplant centers: 250/ year

Type of APAP products

- OTC products: 53% (n=147) used only OTC
  - 96% (n=141): single OTC product
  - 4% (n=6): two OTC products
- Rx products (opioid combo): 44% (n=120) used opioid/APAP products
  - 28% (n=76): Rx only
  - 15% (n=41): Rx and OTC
- Concurrent use of 2 APAP preparations: *22% overall*

Current antidepressant use

- 39% (n=108) ≥1 Rx antidepressant
- 12% (n=34): 2 or 3 simultaneously
- Females>males (46% vs. 20%)
- More likely to take opioid (17% vs. 5%) and opioid/APAP (55% vs. 37%)

Unintentional vs. Intention overdose (Table 2)

- 44% (n=122): intentional
- 48% (n=131): unintentional
  - 79% for pain or constitutional symptoms
  - Many (n or %?) ingested modest amounts of APAP over weeks or months

- 8% (n=22): unclear
- Differences between unintentional vs. intentional:
  - Older patients (median age: 38 yrs vs. 32 yrs)
  - *Multiple APAP products (38% vs. 5%)*
  - Sought care longer after symptoms onset (media days: 4 vs. 1)
  - Less likely to report depression
  - Significantly lower serum APAP level
  - Significantly lower ALT
  - More like to have severe hepatic encephalopathy
  - Similar history of past substance abuse
  - Similar education level
  - 19 patients with unintentional overdose used APAP > 7 days

Opioid/APAP use: (n=120, 44% of 275)

- 63% (n=83 of 131) unintentional, 18% (n=22 of 122) intentional
- 69% (n=83 of 120) were hydrocodone/APAP (Vicodin)
- Clinical indictor of disease severity such as platelets, ALT, bilirubin: lower
- No difference in transplantation rate and overall survival
- *A third of narcotic users were simultaneously ingesting an OTC APAP product (data not shown)*

History of substance abuse:

- Similar between unintentional group (35%) and intentional group (31%)
- Toxicology screens (all drugs of abuse including narcotics):
  - N=77 subjects (28% of 275) available
  - N=58 positive (75% of 77 or 21% of 275):
    - N=10: marijuana
    - N=11: cocaine
    - N=5: amphetamines
    - N=32: opiates, benzodiazepines, barbiturate or TCA or combinations
  - Not distinguished in illegal and legal narcotic use

Alcohol use and Abuse

- Chronic alcohol use: 55%
- Alcohol abuse: 35%
- Alcohol abusers vs. non-abusers
  - lower APAP level
  - less likely to use antidepressants or narcotic combination
  - less likely to present with severe hepatic encephalopathy
- No differences between abusers and abstinent in INR, ALT, bilirubin, BMI, APACHE II score, MELD score or overall survival
- *65% patients with ≤ 4 APAP/day were alcohol abusers and consumed greater alcohol than those taking > 4 g APAP/day (data not shown)*

APAP dose:

- N=19 (7%) took APAP ≤ 4 g/day
- Lower dose vs. higher dose:
  - Older
  - More unintentional
  - More often used or abused alcohol

Outcomes

- N=178 (65%) survived without liver transplantation: no significant differences from non-survivors in serum APAP level, antidepressant use, total APAP dose, type of overdose, narcotic or narcotic combination use, bilirubin, platelets, BMI, sex, age, ethnicity
- N=74 (27%) died
- N=23 (8%) underwent transplantation
- Overall, n=196 (71%) alive at the 3-week outcome point

Summary and Conclusion

1. APAP-related hepatotoxicity accounted for at least 42% acute liver failure cases in the U.S.
2. Intentional and unintentional APAP overdose almost equally contributed to the APAP-related ALF.
3. 44% (n=120 of 275) were related to opioid/APAP combination products, 69% (n=83 of 120) were hydrocodone/APAP products and 30% (n=83 of 275) or 63% (n=83 of 131) were unintentional.
4. Overall 22% of patients simultaneously took 2 APAP preparations.
5. A third of narcotic/APAP users simultaneously took OTC APAP products

Comments:

1. More characterization of acute liver failure cases associated with opioid/APAP combinations are needed to assess any associations of opioid tolerance and physical dependence with opioid/APAP-related unintentional APAP overdose.
2. Unintentional overdose should be further stratified as the "known" overdose (APAP overdose from seeking a more pain relief or overcoming a poor pain relief) and the "unknown" overdose (APAP overdose from mistaking multiple drugs containing APAP that the patients were not aware of).
3. The report did not provide the detailed exposure information of opioid/APAP combination products in the ALF patients, such as duration, dosage, concurrent medications, clinical indication (acute or chronic pain), history of opioid or APAP use and medical history (particularly liver disease).
4. More detailed comparisons in the APAP-related ALF between OTC and Rx products should be performed, including estimated incidences. While the incidence of APAP-related hepatotoxicity can not be calculated due to unknown actual exposure population (denominator) of acetaminophen OTC and Rx products, the population exposed to OTC products would be certainly much larger than that to Rx products based on sales information. Therefore, the hepatotoxicity

rate associated with opioid/APAP combination (mostly contributed by hydrocodone/APAP) would be likely higher than the OTC products.

5. 39% (n=108 of 275) of patients currently took antidepressant use with APAP; potential confounding variable.

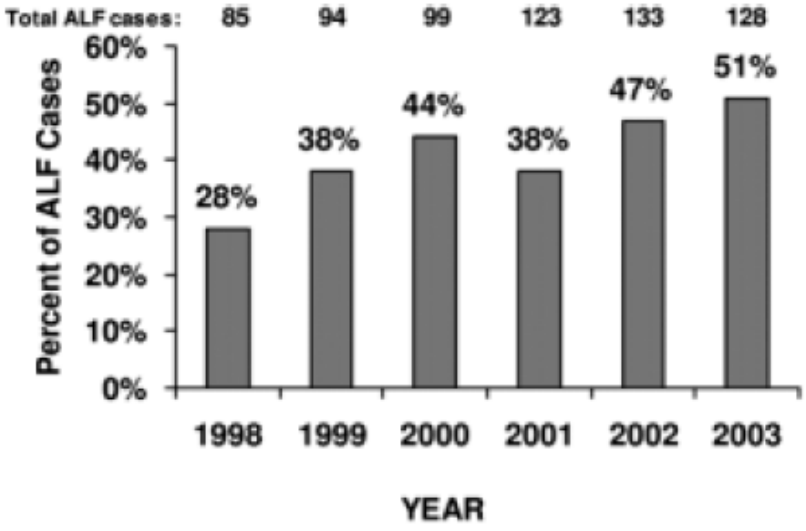


Fig. 1. Proportion of ALF cases attributed to acetaminophen in each of the first 6 years of the ALF Study Group: January 1998 to December 2003.

Table 1. Features of Acetaminophen Overdose ALF Subjects; N = 275

Characteristic	Value
Age (yrs)	37 (17-76)
Sex, n (% female)	204 (74%)
Race	
White	242 (88%)
African American	15 (5%)
Asian	6 (2%)
Hispanic	5 (2%)
Native American	3 (1%)
Other	4 (2%)
Overdose Type	
Unintentional	131 (48%)
Intentional	122 (44%)
Unknown	22 (8%)
Serum acetaminophen level, μg/dL (n = 257)	31 (0-644)
Acetaminophen dose, g (n = 179)	24 (1.2-180)
Alcohol use (n = 273)	151 (55%)
Alcohol abuse (male >40 g/d; female >20 g/d) (n = 196)	68 (35%)
Narcotic/acetaminophen compound use (n = 267)	120 (53%)
OTC Acetaminophen Use (n = 147)	
1 product	141 (51%)
2 products	6 (2%)
Antidepressant use, n (%)	108 (61)
International normalized ratio	3.0 (1.2-27.1)
Bilirubin, mg/dL*	4.5 (0.3-48.2)
Serum ALT, IU/L	4,186 (136-19, 826)
Serum creatinine, mg/dL†	2.0 (0.2-10.5)
Arterial pH	7.42 (6.94-7.9)
Hepatic Coma Grade on admission	
1	84 (31%)
2	52 (19%)
3	63 (23%)
4	72 (27%)
Overall outcome	
Survived without transplant	178 (65%)
Died without transplant	74 (26%)
Transplantation, lived 3 weeks	18 (6%)
Transplantation; died	5 (2%)

NOTE. Median (range) or numbers (%) are presented. Abbreviation: OTC, over-the-counter.

*To convert to mmol/L multiply by 17.1.

†To convert to mmol/L multiply by 88.4.

Table 2. Baseline Features/Outcomes in Intentional and Unintentional Acetaminophen Overdose

	Unintentional Overdose (N = 131)		Intentional Overdose (N = 122)	
Characteristic	Value	No. of Patients Included	Value	No. of Patients Included
Age (years)	38 (18-76)	131	34 (17-68)	122
Sex (% female)	96 (73%)	131	90 (74%)	122
Survival without transplantation	84 (64%)	131	80 (66%)	122
Liver transplantation	12 (9%)	131	8 (7%)	122
Listed for liver transplantation	35 (27%)	130	30 (25%)	122
Days from admission to transplantation	3 (1-7)	11	3 (2-5)	7
Overall short-term (3-week) survival	94 (72%)	131	87 (71%)	122
NAC treatment given	125 (95%)	131	106 (87%)	122
Cause of pain reported*	107 (81%)	116	0 (0%)	122
Total acetaminophen dose (g)	20 (2.5-180)	81	25 (1.2-90)	91
Daily acetaminophen dose (g)	7.5 (1.0-78)	77	25 (1.2-90)	91
Serum acetaminophen (μg/dL)	18 (0-400)	119	64 (0-644)	118
Narcotic/acetaminophen use	83 (63%)	131	22 (18%)	122
Antidepressant use	48 (37%)	131	46 (38%)	122
Serum ALT (U/L)	3,319 (126-18,079)	130	5,326 (179-19,826)	122
Platelets (thousands/μL)	126 (15-699)	131	120 (5-447)	120
Admission Hepatic Coma stage	3 (1-4)	131	2 (1-4)	118
Admission Hepatic Coma (stages 3-4)	72 (55%)	131	47 (39%)	122
Peak hepatic coma stage	3 (1-4)	131	3 (1-4)	120
Peak hepatic coma (stages 3-4)	89 (68%)	131	72 (59%)	122
Met King's criteria	26 (20%)	131	8 (7%)	122
Creatinine $\geq$2	74 (57%)	131	53 (43%)	122
INR $\geq$3	56 (42%)	131	68 (56%)	122
ALT $\geq$3,500	63 (48%)	131	88 (72%)	122
Bilirubin $\geq$4	73 (56%)	131	74 (61%)	122
MELD $\geq$20	113 (88%)	129	102 (87%)	117
APACHE II $\geq$15	75 (66%)	113	49 (57%)	86
BMI	25 (17-51)	97	24 (16-56)	99

NOTE. Median (range) or numbers (%) are presented. 22 subjects could not be classified as suicidal or accidental. Data available for all 275 subjects except as noted (n = xxx).

*Reported causes of pain: chronic pain (n = 33), chronic back pain (n = 24), headache (n = 14), chronic abdominal pain (n = 9), viral URI (n = 7), migraine (n = 9), toothache (n = 6), orthopedic pain (n = 5), fibromyalgia (n = 4), rheumatologic pain (n = 5), chronic pancreatitis (n = 2); postsurgical pain (n = 2), and one each: hangover, earache, fever, menstrual pain; insomnia, leg pain.

Appendix 13. Abuse and Misuse of Opioids

Catherine Dormitzer: CSS Epidemiological Analysis on hydrocodone combination products. Jan 5, 2007

Indication use for hydrocodone products (Able 2): in 2004, the most commonly reported indication for hydrocodone was "back pain," likely chronic in nature.

National Survey on Drug Use and Health (NSDUH) (the *National Household Survey On Drug Abuse* before 2002).

- ***Target:*** US population aged 12 and above
- ***Survey Question:*** *"have you ever, even once, used (pain reliever) that was not prescribed for your or that you took only for the experience or feeling it caused"*.
- ***Abuse ratio:*** number of lifetime non-medical users over the total number of prescription filled for that year.

Drug abuse warning network (DAWN)

An active public health surveillance system that examines drug abuse related emergency room visits and drug abuse related death.

Target: nationally representative sample of non-federal, short-term general hospital that operate 24-hour Emergency Departments; currently 1067 hospitals

Table 2: Projected Top Ten Indications for Hydrocodone, 2004

	Hydrocodone
1	Backache, Unspecified
2	Pain Low Back, not otherwise specified (NOS)
3	Surgery After Bone Disorder, Other
4	Surgery After Hernia
5	Surgery After Musculoskeletal
6	Surgery After Gallbladder Biliary
7	Surgery After Fractures
8	Headache, NOS
9	Sprain/Strain, Neck
10	Sprain, Ankle

NOS indicates – not otherwise specified
Source: IMS Health

Non-medical use of opioids

Table 4: Non-medical Users of Selected Pain Relievers in Lifetime, Numbers in Thousands (Percent US population>12 years) – National Household Survey on Drug Abuse 1999 – 2001

Drug	*1999*	*2000*	*2001*
	Number in Thousands (Percent of Population)		
Hydrocodone Products [1]	6,098 (2.8)	6,746 (3.0)	9,500 (4.2)
Oxycodone Products[2]	6,489 (2.9)	6,392 (2.9)	7,865 (3.5)
Propoxyphene or Codeine Products[3]	14,516 (6.6)	13,542 (6.1)	14,971 (6.6)
"Abuse Ratio"	*Lifetime Non-medical Use per 100 Prescriptions sold*		
Hydrocodone Products [1]	7.5	7.6	9.9
Oxycodone Products[2]	33.7	27.4	29.7
Propoxyphene or Codeine Products[3]	20.0	19.8	22.4

[1] Includes Vicodin®, Lortab®, or Lorcet®, and hydrocodone.
[2] Includes Percocet®, Percodan® or Tylox®.
[3] Includes Darvocet®, Darvon® or Tylenol® with Codeine, codeine, Phenaphen® with Codeine, propoxyphene, and SK-65®.
Sources: SAMHSA, Office of Applied Studies, 1997 -2001 National Household Surveys on Drug Abuse, IMS Health

Table 5: Non-medical Users of Selected Pain Relievers in Lifetime, Numbers in Thousands (Percent US population>12 years) -- National Survey on Drug Use and Health 2002 – 2004

Drug	*2002*	*2003*	*2004*
	Numbers in Thousands (Percent of Population)		
Any Pain Reliever [1]	29,611 (12.6)	31,207 (13.1)	32,101 (16.5)
Hydrocodone Products [1,2]	13,952 (5.9)	16,808 (7.1)	17,878 (7.4)
Oxycodone Products[1,3]	10,151 (4.3)	11,538 (4.9)	12,038 (5.0)
Propoxyphene or Codeine Products[1,4]	20,653 (8.8)	21,428 (9.0)	19,761 (8.2)
"Abuse Ratio"	*Lifetime Non-medical Use per 100 Prescriptions sold*		
Hydrocodone Products [1,2]	13.5	15.1	15.6
Oxycodone Products [1,3]	34.6	35.6	34.5
Propoxyphene or Codeine Products [1,4]	32.4	34.7	34.6

[1] Includes other-specific drug responses that are not asked about explicitly in the Pain Relievers module but fall into this category.
[2] Includes Vicodin®, Lortab®, or Lorcet®, and hydrocodone.
[3] Includes Percocet®, Percodan® or Tylox®, and OxyContin®.
[4] Includes Darvocet®, Darvon® or Tylenol® with Codeine, codeine, Phenaphen® with Codeine, propoxyphene, and SK-65®.
Sources: SAMHSA, Office of Applied Studies, 2002-2004 National Surveys on Drug Use and Health, IMS Health.

Drug abuse-related Emergency Room visits (DAWN emergency room data)

Table 8: Reporting Rate of Emergency Room Visits -- DAWN 1997 -2002

Drug name	*1997*	*1998*	*1999*	*2000*	*2001*	*2002*	*% change 1997 -2002*
DAWN Estimate							
Opioid analgesic combinations	54,116	58,946	69,011	82,373	99,317	119,185	120.2%
Hydrocodone/combinations	11,570	13,611	15,252	20,098	21,567	25,197	117.8%
Oxycodone/combinations	5,012	5,211	6,429	10,825	18,409	22,397	346.9%
Codeine/combinations	7,869	6,620	4,974	5,295	3,720	4,961	-37.0%
Propoxyphene/combinations	6,502	5,826	5,632	5,485	5,361	4,676	-28.1%
Projected Number of Total Prescriptions Dispensed							
Total Hydrocodone Sales	63,626	71,020	81,725	88,778	96,335	103,661	62.9%
Total Oxycodone Sales	13,978	16,183	19,225	23,312	26,513	29,296	109.6%
Total Codeine Sales	40,602	39,318	40,813	37,366	36,461	4,647	-14.7%
Total Propoxyphene Sales	31,589	31,951	31,547	30,992	30,404	29161	-7.7%
ED Reporting Rate*							
Hydrocodone/combinations	18.2	19.2	18.7	22.6	22.4	24.3	33.7%
Oxycodone/combinations	35.9	32.2	33.4	46.4	69.4	76.4	113.2%
Codeine/combinations	19.4	16.8	12.2	14.2	10.2	14.3	-26.1%
Propoxyphene/combinations	20.6	18.2	17.8	17.7	17.6	16.0	-22.1%

* Reporting Rate = ED Mentions/100, 000 Prescriptions Sold
SOURCES: Office of Applied Studies, SAMHSA, Drug Abuse Warning Network, 2002 (03/2003 update), IMS Health

Table 9: National Estimates and Reporting Rate of Non-Medical Use ED Visits per Prescriptions Sold –New DAWN, 2004

2004	*Non-medical Use ED visits*	*Projected Number of Prescriptions*	*Non-medical ED visits per 100,000 prescriptions sold*
Hydrocodone combinations	42,491	114,673	37.1
Oxycodone All combinations	36,559	34,872	104.8
Oxycodone – Immediate Release	14,198	23,933	59.3
Oxycodone – Controlled Release	19,898	10,939	181.8
Codeine combinations	5,836	30,252	19.3
Propoxyphene combinations	6,448	26,899	24.0

Includes cases with multiple drug reports.
SOURCE: Office of Applied Studies, SAMHSA, Drug Abuse Warning Network, IMS Health

Drug abuse-related death (DWAN Medical Examiner Data)

Table 10: Consistent Panel DAWN Medical Examiner Reports of Drug Mentions for 28 Metropolitan Areas

Drug name	1997	1998	1999	2000	2001	2002	2003
Number of Reported Deaths							
Hydrocodone	209	252	295	388	527	579	588
Oxycodone	72	153	218	368	492	594	709
Codeine	1,042	1,067	1,083	1,165	922	974	663
Propoxyphene	326	327	333	364	378	350	282
Estimated of U.S. Dispensed Prescriptions*							
Hydrocodone Rx	63,626	71,020	81,725	88,778	96,335	103,661	111,077
Oxycodone Rx	13,978	16,183	19,225	23,312	26,513	29,296	32,364
Codeine Rx	40,602	39,318	40,813	37,366	36,461	34,647	34,053
Propoxyphene Rx	31,589	31,951	31,547	30,992	30,404	29,161	27,745
Number of Reported Deaths per 100,000 Prescriptions sold‡							
Hydrocodone/combinations	0.3	0.3	0.4	0.4	0.5	0.6	0.5
Oxycodone/combination	0.5	0.9	1.1	1.6	1.9	2.0	2.2
Codeine/combinations	2.6	2.7	2.6	3.1	2.5	2.8	1.9
Propoxyphene/combinations	1.0	1.0	1.1	1.2	1.2	1.2	1.0

‡ Deaths per 100,000 Prescriptions sold
This is a "crude" estimate because ME data do not represent national estimates, while the sales data represents the entire U.S. drug market. Until better analytical tools are developed, these ratios are calculated similarly for each drug and used for comparative purposes only.
SOURCE: Office of Applied Studies, SAMHSA, Drug Abuse Warning Network, 2002 (09/2003 update).

REFERENCES

1. Trescot AM, Boswell MV, Atluri SL, et al. Opioid guidelines in the management of chronic non-cancer pain. *Pain Physician* 2006;9(1):1-39.
2. Gutstein HaA, H. Chapter 21. Opioid Analgesics; 2006.
3. Aronoff DM, Oates JA, Boutaud O. New insights into the mechanism of action of acetaminophen: Its clinical pharmacologic characteristics reflect its inhibition of the two prostaglandin H2 synthases. *Clin Pharmacol Ther* 2006;79(1):9-19.
4. Raffa RB, Clark-Vetri R, Tallarida RJ, Wertheimer AI. Combination strategies for pain management. *Expert Opin Pharmacother* 2003;4(10):1697-708.
5. Raffa RB. Pharmacology of oral combination analgesics: rational therapy for pain. *J Clin Pharm Ther* 2001;26(4):257-64.
6. Beaver WT. Combination analgesics. *Am J Med* 1984;77(3A):38-53.
7. Phero JC, Becker D. Rational use of analgesic combinations. *Dent Clin North Am* 2002;46(4):691-705.
8. Beaver WT, McMillan D. Methodological considerations in the evaluation of analgesic combinations: acetaminophen (paracetamol) and hydrocodone in postpartum pain. *Br J Clin Pharmacol* 1980;10 Suppl 2:215S-23S.
9. Cooper SA, Precheur H, Rauch D, Rosenheck A, Ladov M, Engel J. Evaluation of oxycodone and acetaminophen in treatment of postoperative dental pain. *Oral Surg Oral Med Oral Pathol* 1980;50(6):496-501.
10. Sunshine A, Olson NZ, Colon A, et al. Analgesic efficacy of controlled-release oxycodone in postoperative pain. *J Clin Pharmacol* 1996;36(7):595-603.
11. Edwards JE, Moore RA, McQuay HJ. Single dose oxycodone and oxycodone plus paracetamol (acetominophen) for acute postoperative pain. *Cochrane Database Syst Rev* 2000(4):CD002763.
12. Quiding H, Haggquist SO. Visual analogue scale and the analysis of analgesic action. *Eur J Clin Pharmacol* 1983;24(4):475-8.
13. Gertzbein SD, Tile M, McMurty RY, et al. Analysis of the analgesic efficacy of acetaminophen 1000 mg, codeine phosphate 60 mg, and the combination of acetaminophen 1000 mg and codeine phosphate 60 mg in the relief of postoperative pain. *Pharmacotherapy* 1986;6(3):104-7.
14. Moore A, Collins S, Carroll D, McQuay H. Paracetamol with and without codeine in acute pain: a quantitative systematic review. *Pain* 1997;70(2-3):193-201.
15. Bjune K, Stubhaug A, Dodgson MS, Breivik H. Additive analgesic effect of codeine and paracetamol can be detected in strong, but not moderate, pain after Caesarean section. Baseline pain-intensity is a determinant of assay-sensitivity in a postoperative analgesic trial. *Acta Anaesthesiol Scand* 1996;40(4):399-407.
16. Collins SL, Edwards JE, Moore RA, McQuay HJ. Single dose dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative pain. *Cochrane Database Syst Rev* 2000(2):CD001440.
17. Collins SL, Edwards JE, Moore RA, McQuay HJ. Single-dose dextropropoxyphene in post-operative pain: a quantitative systematic review. *Eur J Clin Pharmacol* 1998;54(2):107-12.
18. Li Wan Po A, Zhang WY. Systematic overview of co-proxamol to assess analgesic effects of addition of dextropropoxyphene to paracetamol. *Bmj* 1997;315(7122):1565-71.
19. Litkowski LJ, Christensen SE, Adamson DN, Van Dyke T, Han SH, Newman KB. Analgesic efficacy and tolerability of oxycodone 5 mg/ibuprofen 400 mg compared with those of oxycodone 5 mg/acetaminophen 325 mg and hydrocodone 7.5 mg/acetaminophen 500 mg in patients with moderate to severe postoperative pain: a randomized, double-blind, placebo-

controlled, single-dose, parallel-group study in a dental pain model. *Clin Ther* 2005;27(4):418-29.
20. Fricke JR, Jr., Karim R, Jordan D, Rosenthal N. A double-blind, single-dose comparison of the analgesic efficacy of tramadol/acetaminophen combination tablets, hydrocodone/acetaminophen combination tablets, and placebo after oral surgery. *Clin Ther* 2002;24(6):953-68.
21. White PF, Joshi GP, Carpenter RL, Fragen RJ. A comparison of oral ketorolac and hydrocodone-acetaminophen for analgesia after ambulatory surgery: arthroscopy versus laparoscopic tubal ligation. *Anesth Analg* 1997;85(1):37-43.
22. Marco CA, Plewa MC, Buderer N, Black C, Roberts A. Comparison of oxycodone and hydrocodone for the treatment of acute pain associated with fractures: a double-blind, randomized, controlled trial. *Acad Emerg Med* 2005;12(4):282-8.
23. Gimbel JS, Brugger A, Zhao W, Verburg KM, Geis GS. Efficacy and tolerability of celecoxib versus hydrocodone/acetaminophen in the treatment of pain after ambulatory orthopedic surgery in adults. *Clin Ther* 2001;23(2):228-41.
24. Hewitt DJ, Todd KH, Xiang J, Jordan DM, Rosenthal NR. Tramadol/Acetaminophen or Hydrocodone/Acetaminophen for the Treatment of Ankle Sprain: A Randomized, Placebo-Controlled Trial. *Ann Emerg Med* 2006.
25. Church CA, Stewart Ct, TJ OL, Wallace D. Rofecoxib versus hydrocodone/acetaminophen for postoperative analgesia in functional endoscopic sinus surgery. *Laryngoscope* 2006;116(4):602-6.
26. Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. *Pain* 2004;112(3):372-80.
27. Moore RA, McQuay HJ. Prevalence of opioid adverse events in chronic non-malignant pain: systematic review of randomised trials of oral opioids. *Arthritis Res Ther* 2005;7(5):R1046-51.
28. Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E. Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. *Cmaj* 2006;174(11):1589-94.
29. Martell BA, O'Connor PG, Kerns RD, et al. Systematic review: opioid treatment for chronic back pain: prevalence, efficacy, and association with addiction. *Ann Intern Med* 2007;146(2):116-27.
30. Caldwell JR, Hale ME, Boyd RE, et al. Treatment of osteoarthritis pain with controlled release oxycodone or fixed combination oxycodone plus acetaminophen added to nonsteroidal antiinflammatory drugs: a double blind, randomized, multicenter, placebo controlled trial. *J Rheumatol* 1999;26(4):862-9.
31. Boureau F, Boccard E. Placebo-controlled study of the analgesic efficacy of a combination of paracetamol and codeine in rheumatoid arthritis *Acta Therapeutica* 1991;17(2):123-36.
32. Kuntz D, Brossel R. [Analgesic effect and clinical tolerability of the combination of paracetamol 500 mg and caffeine 50 mg versus paracetamol 400 mg and dextropropoxyphene 30 mg in back pain]. *Presse Med* 1996;25(25):1171-4.
33. Muller FO, Odendaal CL, Muller FR, Raubenheimer J, Middle MV, Kummer M. Comparison of the efficacy and tolerability of a paracetamol/codeine fixed-dose combination with tramadol in patients with refractory chronic back pain. *Arzneimittelforschung* 1998;48(6):675-9.
34. Skoulis NP, James RC, Harbison RD, Roberts SM. Perturbation of glutathione by a central action of morphine. *Toxicology* 1989;57(3):287-302.
35. Skoulis NP, James RC, Harbison RD, Roberts SM. Depression of hepatic glutathione by opioid analgesic drugs in mice. *Toxicol Appl Pharmacol* 1989;99(1):139-47.
36. Roberts SM, Skoulis NP, James RC. A centrally-mediated effect of morphine to diminish hepatocellular glutathione. *Biochem Pharmacol* 1987;36(18):3001-5.

37. James RC, Goodman DR, Harbison RD. Hepatic glutathione and hepatotoxicity: changes induced by selected narcotics. *J Pharmacol Exp Ther* 1982;221(3):708-14.
38. James RC, Harbison RD. Hepatic glutathione and hepatotoxicity: effects of cytochrome P-450 complexing compounds SKF 525-A, L-alpha acetylmethadol (LAAM), norLAAM, and piperonyl butoxide. *Biochem Pharmacol* 1982;31(10):1829-35.
39. Shayiq RM, Roberts DW, Rothstein K, et al. Repeat exposure to incremental doses of acetaminophen provides protection against acetaminophen-induced lethality in mice: an explanation for high acetaminophen dosage in humans without hepatic injury. *Hepatology* 1999;29(2):451-63.
40. Watkins PB, Kaplowitz N, Slattery JT, et al. Aminotransferase elevations in healthy adults receiving 4 grams of acetaminophen daily: a randomized controlled trial. *Jama* 2006;296(1):87-93.
41. Larson AM, Polson J, Fontana RJ, et al. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. *Hepatology* 2005;42(6):1364-72.
42. Bhamb B, Brown D, Hariharan J, Anderson J, Balousek S, Fleming MF. Survey of select practice behaviors by primary care physicians on the use of opioids for chronic pain. *Curr Med Res Opin* 2006;22(9):1859-65.
43. Adams EH, Breiner S, Cicero TJ, et al. A comparison of the abuse liability of tramadol, NSAIDs, and hydrocodone in patients with chronic pain. *J Pain Symptom Manage* 2006;31(5):465-76.
44. Hall AH, Kulig KW, Rumack BH. Acetaminophen and alcoholics. *DigDis Sci* 1987;32(5):558.
45. Gill EJ, Contos MJ, Peng TC. Acute fatty liver of pregnancy and acetaminophen toxicity leading to liver failure and postpartum liver transplantation. A case report. *J Reprod Med* 2002;47(7):584-6.
46. Metabolic bioactivation can cause idiosyncratic drug reactions. *Drugs and Therapy Perspectives* 1997;9(10):11-3.
47. Altomare E, Vendemiale G, Albano O. Hepatic glutathione content in patients with alcoholic and non alcoholic liver diseases. *Life Sci* 1988;43(12):991-8.
48. Chary S, Goughnour BR, Moulin DE, Thorpe WR, Harsanyi Z, Darke AC. The dose-response relationship of controlled-release codeine (Codeine Contin) in chronic cancer pain. *J Pain Symptom Manage* 1994;9(6):363-71.
49. Fricke J, Halladay SC, Bynum L, Francisco CA. Pain relief after dental impaction surgery using ketorolac, hydrocodone plus acetaminophen, or placebo. *Clin Ther* 1993;15(3):500-9.
50. Forbes JA, Bates JA, Edquist IA, et al. Evaluation of two opioid-acetaminophen combinations and placebo in postoperative oral surgery pain. *Pharmacotherapy* 1994;14(2):139-46.
51. Gammaitoni AR, Galer BS, Bulloch S, et al. Randomized, double-blind, placebo-controlled comparison of the analgesic efficacy of oxycodone 10 mg/acetaminophen 325 mg versus controlled-release oxycodone 20 mg in postsurgical pain. *J Clin Pharmacol* 2003;43(3):296-304.
52. Sunshine A, Olson NZ, Zighelboim I, De Castro A. Ketoprofen, acetaminophen plus oxycodone, and acetaminophen in the relief of postoperative pain. *Clin Pharmacol Ther* 1993;54(5):546-55.
53. Moir MS, Bair E, Shinnick P, Messner A. Acetaminophen versus acetaminophen with codeine after pediatric tonsillectomy. *Laryngoscope* 2000;110(11):1824-7.
54. Macleod AG, Ashford B, Voltz M, et al. Paracetamol versus paracetamol-codeine in the treatment of post-operative dental pain: a randomized, double-blind, prospective trial. *Aust Dent J* 2002;47(2):147-51.
55. Skoglund LA, Skjelbred P, Fyllingen G. Analgesic efficacy of acetaminophen 1000 mg, acetaminophen 2000 mg, and the combination of acetaminophen 1000 mg and codeine

phosphate 60 mg versus placebo in acute postoperative pain. *Pharmacotherapy* 1991;11(5):364-9.
56. Forbes JA, Kehm CJ, Grodin CD, Beaver WT. Evaluation of ketorolac, ibuprofen, acetaminophen, and an acetaminophen-codeine combination in postoperative oral surgery pain. *Pharmacotherapy* 1990;10(6 (Pt 2)):94S-105S.
57. Breivik EK, Barkvoll P, Skovlund E. Combining diclofenac with acetaminophen or acetaminophen-codeine after oral surgery: a randomized, double-blind single-dose study. *Clin Pharmacol Ther* 1999;66(6):625-35.
58. Glowinski J, Boccard E. Placebo-controlled study of the analgesic efficacy of a paracetamol 500 mg/Codeine 30 mg combination together with low-dose vs high-dose diclofenac in rheumatoid arthritis. *Clinical Drug Investigation* 1999;18(3):189-97.

Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

PID#: 2006-23

DATE: November 30, 2006

FROM: Laura A. Governale, Pharm.D., MBA / Drug Use Data Specialist Team Leader
Division of Surveillance, Research and Communication Support
Office of Surveillance and Epidemiology

THROUGH: Solomon Iyasu, MD, MPH, Director
Division of Surveillance, Research and Communication Support
Office of Surveillance and Epidemiology

TO: Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation
Office of Surveillance and Epidemiology

Charles Ganley, M.D., Director
Office of Non-Prescription Drug Products

Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia and Rheumatology Drug Products
Office of New Drugs

SUBJECT: OTC and prescription combination APAP use

****This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.****

EXECUTIVE SUMMARY

In response to a request for drug use data by the Division of Drug Risk Evaluation (DDRE), this consult examines the over-the-counter (OTC) and prescription utilization of acetaminophen (APAP) containing products from years 2001 through 2005. Proprietary drug use databases licensed by the FDA were used to conduct this analysis.

The use, as measured by units sold, for prescription and OTC APAP containing products grew by 17% from year 2001 to 2005. The sale of OTC APAP products grew by 6% from year 2001 to year 2005, while the sale of prescription APAP containing products increased by 38%.

The majority of OTC APAP products are found in combination with other active ingredients (56% combination APAP products versus 44% single-ingredient APAP products). The sale of OTC single-ingredient APAP drug products decreased by approximately 1.5% while combination APAP products increased by approximately 13% from year 2001 to year 2005.

For OTC single-ingredient APAP products, the systemic oral solid regular dosage form accounted for 60% of the market whereas the oral solid long-acting dosage form accounted for 12% of the market during year 2005. The systemic oral solid long-acting dosage form increased by three-fold from year 2001 to 2005.

For OTC combination APAP products, the systemic oral liquid dosage form increased by 34% from year 2001 to year 2005. The most common active ingredient found in combination with APAP was pseudoephedrine.

For prescription APAP containing products, hydrocodone/APAP products accounted for over 57% of all dispensed prescriptions in this market, and has been the number one dispensed prescription product in the entire market of retail dispensed prescriptions since 1997. During year 2005, the codeine and combination non-injectable class (USC5 02232) was the most dispensed class of APAP containing products for all age groups except for the age 0-5 year band which had the highest number of dispensed prescriptions for the acetaminophen class (USC5 02120) of products. The extent of co-use of OTC and prescription APAP products may be underestimated in this analysis due to limitations in data collection

INTRODUCTION

In response to a request for drug use data by the Division of Drug Risk Evaluation (DDRE), this consult examines the over-the-counter (OTC) and prescription utilization of acetaminophen (APAP) containing products from years 2001 through 2005. Utilization information on APAP was requested as background material in preparation for the National Institutes of Health Workshop on Acute Liver Failure on December 4-5, 2006. The meeting will assess current knowledge about acute liver failure (ALF) and include discussions on APAP as a cause of liver injury, intentional versus unintentional APAP overdose, and the role of APAP as a cause of acute liver injury in children.

In support of this meeting, this review provides an overview of the sale of OTC combination and single-ingredient APAP products as well as the trends in outpatient usage for prescription APAP combination products for years 2001 through 2005. Proprietary drug use databases licensed by the FDA were used to conduct this analysis.

METHODS

Because the focus of the NIH workshop is on acute liver failure which primarily manifests in the outpatient setting, we chose to focus this review on the OTC and outpatient prescription use of APAP containing products. In the United States, approximately 2000 cases of acute liver failure occur annually and drugs account for over 50% of them (39% are due to acetaminophen, 13% are idiosyncratic reactions due to other medications). Drugs account for 2-5% of cases of patients hospitalized with jaundice and approximately 10% of all cases of acute hepatitis[1].

For OTC APAP containing products, outpatient use was measured using the IMS Health, IMS National Sales Perspectives™ data (see Appendix 1). Extended units (tablets/capsules/milliliters of solution) of APAP products sold from the manufacturers into the various retail and non-retail channels of distribution were analyzed from years 2001 through 2005. APAP products were categorized as single-ingredient versus combination and analyzed by class and dosage forms.

For prescription APAP containing products, outpatient use and patient demographics were measured using the Verispan, LLC: Vector One®: National (VONA) and indications for use were obtained from the Physician's Drug and Diagnosis Audit (PDDA) (see Appendix 1). Through these sources, estimates of the number of dispensed prescriptions by retail pharmacies and the number of drug mentions by office-based physicians were analyzed from years 2001 through 2005. Prescription APAP containing products were all categorized as combination and analyzed by class, prescribing specialty, patient age[2] and indications for use; there are no prescription-strength single-ingredient APAP products, however, any OTC APAP products may be dispensed as a prescription under a physician's order.

[1] Mehta N, Ozick L. Drug Induced Hepatotoxicity. Emedicine [serial on the internet]. 2006 July [cited 2006 Nov 9]; Available from: http://www.emedicine.com/med/topic3718.htm

[2] Analysis of prescription usage by patient age was conduced for years 2002 through year 2005. Patient demographic factors are not available before year 2002 in Verispan, VONA.

RESULTS

Overall APAP Use

The sale of prescription and OTC APAP containing products appears to be increasing from year 2001 to 2005 (Table 1). Approximately 29 billion extended units (tablets/capsules/milliliters of solution) of APAP products were sold to retail and non-retail pharmacies during year 2005, an increase of 17% since year 2001. Of these, approximately 17.5 billion extended units (61.4%) were over-the-counter (OTC) combination and single-ingredient APAP products and 11 billion (38.6%) were prescription combination APAP products. The sale of all OTC APAP containing products increased by 6% whereas the sale of prescription APAP containing products realized a growth of 38% from year 2001 to 2005.

Table 1: Sale of OTC and prescription APAP containing drug products sold from manufacturers to retail† and non-retail‡ channels of distribution from year 2001 through 2005.

	Extended Units (in thousands)					*% Change from 2001 to 2005*
	2001	**2002**	**2003**	**2004**	**2005**	
Rx and OTC APAP	24,460,290	25,377,600	27,687,155	26,193,116	28,533,925	*16.7%*
OTC APAP All	16,486,034	16,497,200	17,897,267	15,895,272	17,519,525	*6.3%*
Combination	8,589,645	8,628,253	9,510,219	8,438,389	9,743,544	*13.4%*
Single-Ingredient	7,896,389	7,868,947	8,387,048	7,456,883	7,775,981	*-1.5%*
Rx APAP All	7,974,256	8,880,400	9,789,889	10,297,837	11,014,400	*38.1%*
Combination	7,974,256	8,880,400	9,789,889	10,297,837	11,014,400	*38.1%*

IMS Health, IMS National Sales Perspectives™, Years 2001 – 2005; Source file: 0609AP01.dvr

† **Retail** channels include chain, independent, foodstore, mail order, discount houses, and mass merchandiser pharmacies in the entire United States.

‡ **Non-retail** channels include hospitals, long-term care facilities, clinics, home health care providers, and HMOs in the entire United States.

Over-the-Counter APAP Products

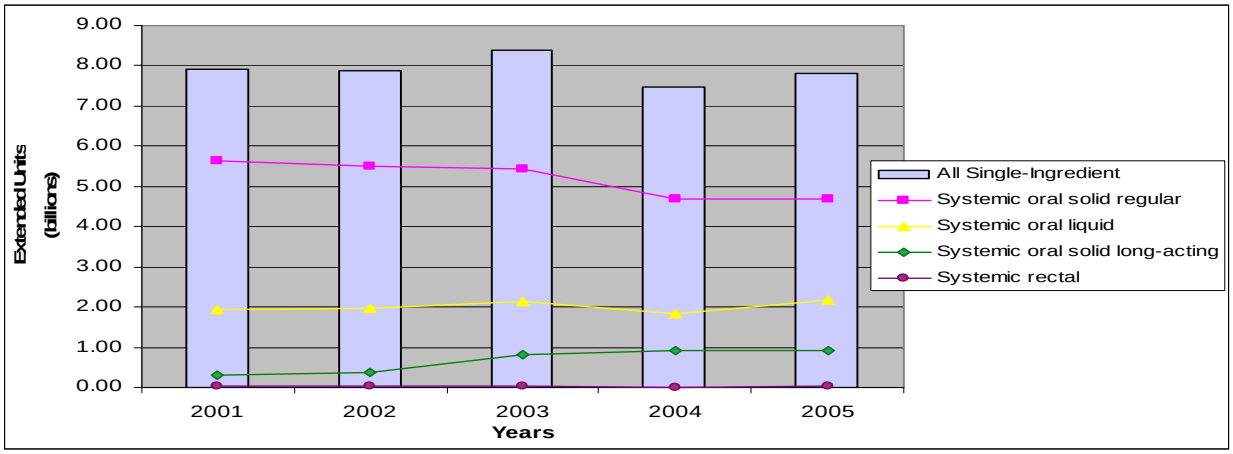
Single-Ingredient APAP

From year 2001 to year 2005, the sale of single-ingredient APAP drug products decreased by approximately 1.5% while the sale of OTC combination APAP products increased by approximately 13% during the same time period (Table 1). The single-ingredient APAP products accounted for approximately 44% of the OTC APAP market in year 2005. (Table 2, Figure 1). Of these products, almost three-quarters were systemic oral solid dosage forms (60% oral solid regular, 12% oral solid long-acting). The long–acting systemic oral solid dosage form increased by three-fold from approximately 4% of the single-ingredient market in year 2001 to 12% in year 2005. Systemic oral liquids made up approximately 28% of the single-ingredient APAP market in year 2005, which grew 12% in market share since year 2001. Of these, the elixir dosage form represented almost 36% of the systemic oral liquid market, followed by the ready-made oral suspensions with approximately 28% of the liquid market (data not shown). In contrast, the oral solid regular dosage form has been decreasing in market share from approximately 71% of the market in year 2001 to 60% of the single-ingredient APAP market in year 2005, a decrease of 17%. The systemic rectal formulation accounted for less than 1% of the single-ingredient APAP market share throughout the observed time period.

Table 2: Total sale of OTC and prescription APAP products by dosage form, Years 2001 - 2005										
	2001		2002		2003		2004		2005	
	N (000)	%	N (000)	%	N (000)	%	N (000)	%	N (000)	%
All APAP Products	**24,427,678**	***100***	**25,343,794**	***100***	**27,657,154**	***100***	**26,172,644**	***100***	**28,544,136**	***100***
OTC APAP	**16,453,423**	***67.4***	**16,463,393**	***65***	**17,867,265**	***64.6***	**15,874,721**	***60.7***	**17,528,402**	***61.4***
COMBINATION APAP	8,557,034	*52*	8,594,447	*52.2*	9,480,217	*53.1*	8,417,556	*53*	9,730,107	*55.5*
SYSTEMIC ORAL LIQUID	4,617,008	*54*	4,653,212	*54.1*	5,364,498	*56.6*	4,849,657	*57.6*	6,188,046	*63.6*
SYSTEMIC ORAL SOLID REG	3,937,507	*46*	3,939,192	*45.8*	4,113,814	*43.4*	3,566,292	*42.4*	3,540,631	*36.4*
SYSTEMIC ORAL SOLID L/A	2,494	*0*	2,042	*0*	1,905	*0*	1,606	*0*	921	*0*
SYSTEMIC ALL OTHERS	26	*0*	0	*0*		*0*		*0*	509	*0*
MOUTH/THROAT TOPICAL	0	*0*	0	*0*		*0*		*0*		*0*
SINGLE-INGREDIENT APAP	7,896,389	*48*	7,868,947	*47.8*	8,387,048	*46.9*	7,457,165	*47*	7,798,295	*44.5*
SYSTEMIC ORAL SOLID REG	5,638,789	*71.4*	5,488,969	*69.8*	5,436,480	*64.8*	4,687,666	*62.9*	4,678,575	*60*
SYSTEMIC ORAL LIQUID	1,942,623	*24.6*	1,980,577	*25.2*	2,123,798	*25.3*	1,824,291	*24.5*	2,169,660	*27.8*
SYSTEMIC ORAL SOLID L/A	297,141	*3.8*	380,134	*4.8*	808,055	*9.6*	928,427	*12.5*	932,211	*12*
SYSTEMIC RECTAL	17,836	*0.2*	19,267	*0.2*	18,715	*0.2*	16,781	*0.2*	17,848	*0.2*
PRESCRIPTION	**7,974,256**	***32.6***	**8,880,400**	***35***	**9,789,889**	***35.4***	**10,297,923**	***39.3***	**11,015,734**	***38.6***
COMBINATION APAP	7,974,256	*100*	8,880,400	*100*	9,789,889	*100*	10,297,916	*100*	11,015,734	*100*
SYSTEMIC ORAL SOLID REG	7,207,325	*90.4*	8,056,496	*90.7*	8,885,381	*90.8*	9,450,071	*91.8*	10,091,896	*91.6*
SYSTEMIC ORAL LIQUID	766,035	*9.6*	823,881	*9.3*	904,497	*9.2*	847,734	*8.2*	922,917	*8.4*
SYSTEMIC ORAL SOLID L/A	895	*0*	23	*0*	11	*0*	111	*0*	921	*0*

IMS Health, IMS National Sales Perspectives™, Retail and Non-Retail, Years 2001 - 2005, Extracted November 2006; Source file: 0611apa1.dvr

Figure 1: Sale of OTC *single-ingredient* APAP products by dosage forms, Years 2001 - 2005[3]

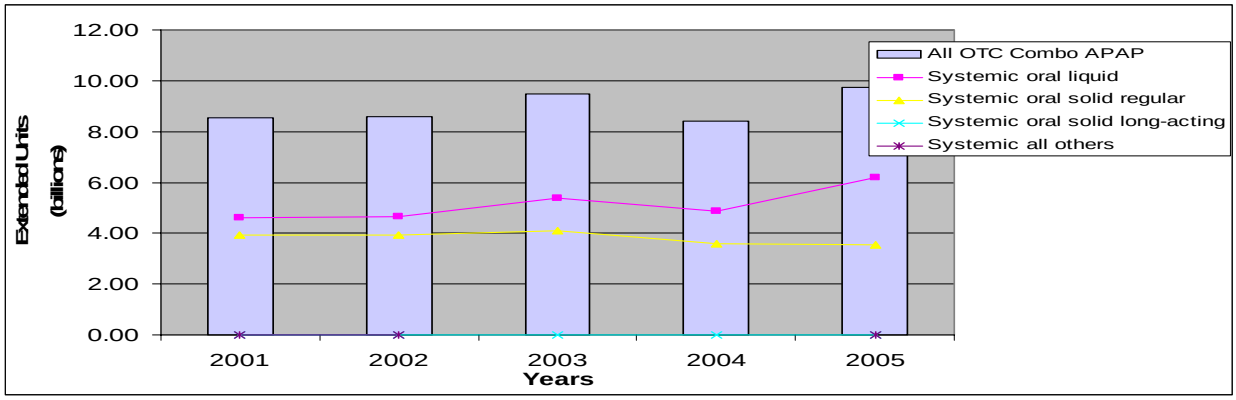


Combination APAP

Combination APAP drug products accounted for approximately 56% of the OTC APAP market share in year 2005 (Table 2, Figure 2). Of these, the systemic oral liquid formation represented approximately 64% of the combination APAP market share in year 2005 which grew from 54% in year 2001. This represented an increase of 34% from year 2001 to year 2005. The oral solid regular formulation decreased from approximately 46% of the market in year 2001 to 36% of the market in year 2005, a decrease of 10%. In contrast to the single-ingredient market, the share of the long-acting oral solid dosage form was negligible in the combination APAP market (see Figure 2).

[3] IMS Health, IMS National Sales Perspectives™ Retail and Non-Retail, Years 2001 – 2005, Extracted November 2006; Source file: 0611apa1.dvr.

Figure 2: Sale of OTC *combination* APAP products by dosage form, Years 2001 - 2005[2]



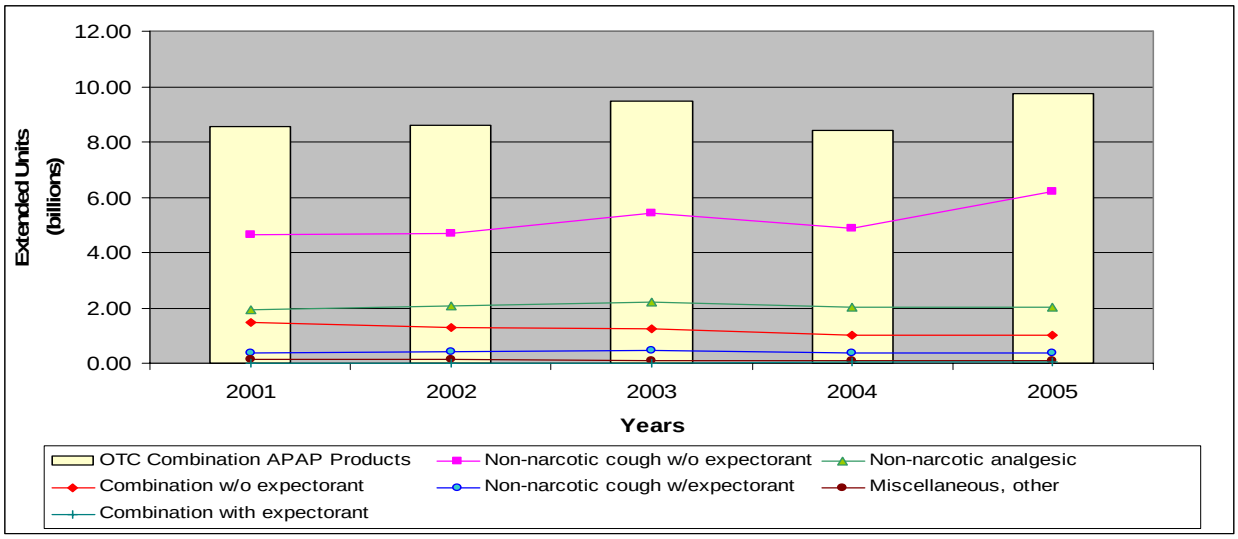
Examining class trends for the OTC combination APAP market, the non-narcotic cough/cold combination without expectorants was the market leader with approximately 64% of the market share in year 2005 (Table 3, Figure 3, see Appendix 2 for list of active ingredients in USC class) relative to 54% of the market share in 2001. During the study period, the number of extended units for this class increased by 34% from approximately 4.6 billion extended units in year 2001 to over 6.2 billion extended units by the end of this study period. This was followed by the analgesic non-narcotic class with approximately 21% of the market share in year 2005. Other classes in the OTC combination market accounted for approximately 15% of the total sale of OTC combination APAP products.

Table 3: Total sale of OTC and prescription APAP products by USC drug classification, Years 2001 - 2005

	2001		2002		2003		2004		2005	
	N (000)	%	N (000)	%	N (000)	%	N (000)	%	N (000)	%
All APAP Products	24,427,678	100	25,343,794	100	27,657,154	100	26,172,644	100	28,544,136	100
OTC APAP	16,453,423	67.4	16,463,393	65	17,867,265	64.6	15,874,721	60.7	17,528,402	61.4
COMBINATION	8,557,034	52	8,594,447	52.2	9,480,217	53.1	8,417,556	53	9,730,107	55.5
34500 NON-NARC COUGH COMB W/O	4,648,534	54.3	4,689,168	54.6	5,437,772	57.4	4,880,884	58	6,226,918	64
02100 ANALG NON-NARCOTIC	1,910,157	22.3	2,090,694	24.3	2,186,789	23.1	2,039,237	24.2	2,014,075	20.7
14300 COMB W/O EXPECTORANT	1,463,322	17.1	1,289,354	15	1,251,555	13.2	999,181	11.9	993,386	10.2
34600 N-N COUGH COMB W/EXP	384,798	4.5	395,941	4.6	471,767	5	375,595	4.5	373,397	3.8
78800 MISCELLANEOUS,OTH	132,746	1.6	117,575	1.4	104,650	1.1	91,816	1.1	87,315	0.9
14500 COMB W/EXPECTORANT	15,454	0.2	7,728	0.1	22,160	0.2	27,558	0.3	32,202	0.3
09100 ANTIARTH,SYSTEMIC	1,136	0	3,175	0	4,701	0	2,098	0	1,866	0
05100 ANTACIDS, PLAIN		0		0	24	0	604	0	714	0
67200 NON-BARB	872	0	811	0	800	0	583	0	234	0
28200 RESPIRATORY NSAID	16	0	0	0		0		0		0
PLAIN	7,896,389	48	7,868,947	47.8	8,387,048	46.9	7,457,165	47	7,798,295	44.5
02100 ANALG NON-NARCOTIC	7,894,150	100	7,867,374	100	8,386,985	100	7,457,165	100	7,798,295	100
34500 NON-NARC COUGH COMB W/O	2,239	0	1,573	0	63	0	0	0		0
Prescription	7,974,256	32.6	8,880,400	35	9,789,889	35.4	10,297,923	39.3	11,015,734	38.6
COMBINATION	7,974,256	100	8,880,400	100	9,789,889	100	10,297,916	100	11,015,734	100
02200 ANALG NARCOTIC	7,537,512	94.5	8,214,004	92.5	9,035,013	92.3	9,499,970	92.3	10,217,063	92.7
02100 ANALG NON-NARCOTIC	433,989	5.4	664,656	7.5	753,100	7.7	795,914	7.7	795,929	7.2
59100 MUSCLE RELAXANTS	785	0	926	0	947	0	1,129	0	1,504	0
14300 COMB W/O EXPECTORANT	1,129	0	63	0	102	0	278	0	1,156	0
34200 NARC COUGH COMB W/O EXP	839	0	751	0	727	0	624	0	80	0
14500 COMB W/EXPECTORANT		0		0		0		0	2	0
34600 N-N COUGH COMB W/EXP	3	0		0		0		0		0
PLAIN		0		0		0	8	0		0
78100 CRUDE DRUGS & CHEMICALS		0		0		0	8	100		0

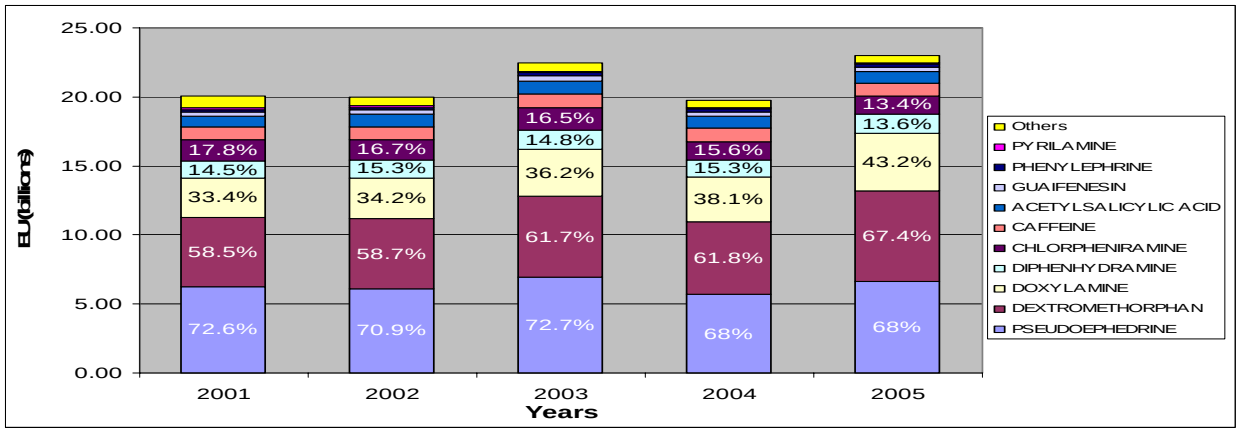
IMS Health, IMS National Sales Perspectives™, Retail and Non-Retail, Years 2001 - 2005, Extracted November 2006; Source file: 0611apa2.dvr

Figure 3: Sale of the top 6 OTC combination APAP products by drug class, Years 2001 - 2005[4]



When examining these combination APAP products by active ingredient, pseudoephedrine was the most common active ingredient found in these combination APAP products appearing in 68% of the combination market followed by dextromethorphan with 67% during year 2005 (Figure 4). Since multiple active ingredients can be found in combination APAP products, the percentages do not add up to 100%.

Figure 4: Sale of OTC APAP Combination Products by Ingredient, Years 2001 – 2005[5]



Prescription APAP-containing Products

Prescription APAP containing products were all categorized as combination and analyzed by class, prescribing specialty, patient demographics and indications for use; there are no prescription single-ingredient APAP products. All prescription APAP products are combination APAP products except for those OTC APAP products dispensed under a physician's order.

[4] IMS Health, IMS National Sales Perspectives™ Retail and Non-Retail, Years 2001 – 2005, Extracted November 2006; Source file: 0611apa2.dvr.
[5] IMS Health, IMS National Sales Perspectives™ Retail and Non-Retail, Years 2001 – 2005, Extracted July 2006; Source file: 0607apap.dvr.

Class trends

Analysis of dispensed prescriptions showed that during the 5 year study period, the codeine and combination non-injectable class accounted for the largest market share for all prescription APAP combination products (Table 4, see Appendix 3 for drug grouping classifications). During year 2001, approximately 120 million prescriptions were dispensed in this class, representing approximately 74% of the total combination APAP market share. By year 2005, dispensed prescriptions in this class had increased by approximately 21% to over 144 million prescriptions, representing approximately 79% of the total market for combination APAP products. Hydrocodone/APAP products accounted for approximately 72% and oxycodone/APAP products accounted for nearly 17% of all products dispensed in this class during year 2005 (data not shown).

The propoxyphene class was the second most dispensed class of prescription combination APAP products with nearly 13% of the market share or over 23 million dispensed prescriptions for all prescription APAP combination products during year 2005. The number of prescriptions dispensed for this class declined by nearly 17% from year 2001 from 28 million dispensed prescriptions which accounted for approximately 17% of the market share for all prescription APAP combination products during that year.

Table 4: Total number of dispensed prescriptions (in thousands) for APAP containing drug products by class, Years 2001 – 2005.

	2001		2002		2003		2004		2005	
	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*
	(000)	*%*	(000)	*%*	(000)	*%*	(000)	*%*	(000)	*%*
TOTAL MARKET	**161,154**	***100.0%***	**165,577**	***100.0%***	**169,692**	***100.0%***	**174,496**	***100.0%***	**182,287**	***100.0%***
Codeine & Comb Non-Inj	119,744	*74.3%*	124,339	*75.1%*	129,330	*76.2%*	135,613	*77.7%*	144,560	*79.3%*
Propoxyphenes	28,070	*17.4%*	26,221	*15.8%*	25,227	*14.9%*	24,285	*13.9%*	23,388	*12.8%*
Acetaminophen	10,481	*6.5%*	8,868	*5.4%*	8,359	*4.9%*	7,565	*4.3%*	7,299	*4.0%*
Syn, Non-Narc Non-Inj	606	*0.4%*	4,185	*2.5%*	5,115	*3.0%*	5,454	*3.1%*	5,615	*3.1%*
Anti-Migraine, Comb	2,252	*1.4%*	1,964	*1.2%*	1,655	*1.0%*	1,544	*0.9%*	1,344	*0.7%*
Syn, Non-Narc Combo	0	*0.0%*	--	--	6	*0.0%*	34	*0.0%*	80	*0.0%*
Cold w/ Analgesics	1	*0.0%*	0	*0.0%*	0	*0.0%*	1	*0.0%*	1	*0.0%*

Verispan, VONA: Years 2001 – 2005, Extracted November 2006. Source file: 2006-23 APAP class molecule.qry

Active ingredient trends

Examination of dispensed prescriptions by active ingredient showed that hydrocodone/APAP products were by far the most commonly dispensed prescription of all combination APAP products during year 2005 (Table 5). This trend has been increasing from over 80 million dispensed prescription (50% of all combination APAP market) in year 2001 to over 104 million dispensed prescriptions (57% of all combination APAP market) in year 2005. This is also true when looking at the entire market for dispensed prescription products; the combination hydrocodone/APAP product is the number 1 most frequently dispensed prescription product in the U.S. since 1997 (data not shown)[6]. In year 2005, hydrocodone/APAP product accounted for approximately 3.2% of the entire dispensed prescription market.

[6] Verispan, VONA: Years 1996 – 2005, Extracted November 2006; Source file: 2006-23 TM96-05 Products.qry

Table 5: Top 10 most frequently dispensed prescription APAP containing products (in thousands) from year 2001 – 2005.

	2001		2002		2003		2004		2005	
	TRxs (000)	*Share* %	TRxs (000)	*Share* %	TRxs (000)	*Share* %	TRxs (000)	*Share* %	TRxs (000)	*Share* %
TOTAL MARKET	**161,154**	***100.0%***	**165,577**	***100.0%***	**169,692**	***100.0%***	**174,496**	***100.0%***	**182,287**	***100.0%***
hydrocodone/APAP	80,492	*49.9%*	86,081	*52.0%*	90,890	*53.6%*	96,571	*55.3%*	104,199	*57.2%*
oxycodone hcl/acetaminophen	16,724	*10.4%*	18,025	*10.9%*	19,835	*11.7%*	21,729	*12.5%*	24,022	*13.2%*
propoxyphene napsylate/APAP	27,603	*17.1%*	25,859	*15.6%*	24,924	*14.7%*	23,916	*13.7%*	23,073	*12.7%*
codeine/APAP	22,127	*13.7%*	19,834	*12.0%*	18,203	*10.7%*	16,913	*9.7%*	15,924	*8.7%*
tramadol hcl/acetaminophen	377	*0.2%*	4,000	*2.4%*	4,973	*2.9%*	5,337	*3.1%*	5,509	*3.0%*
APAP/caffeine/butalb	5,841	*3.6%*	5,410	*3.3%*	5,180	*3.1%*	5,103	*2.9%*	4,738	*2.6%*
acetaminophen	3,988	*2.5%*	2,856	*1.7%*	2,670	*1.6%*	2,015	*1.2%*	2,202	*1.2%*
apap/isometheptene/dichlphen	2,252	*1.4%*	1,964	*1.2%*	1,655	*1.0%*	1,544	*0.9%*	1,344	*0.7%*
codeine/apap/caffein/butalb	402	*0.2%*	400	*0.2%*	402	*0.2%*	400	*0.2%*	414	*0.2%*
acetaminophen/butalbital	561	*0.3%*	495	*0.3%*	400	*0.2%*	364	*0.2%*	326	*0.2%*
All Others	788	*0.5%*	654	*0.4%*	560	*0.3%*	599	*0.3%*	527	*0.3%*

Verispan, VONA: Years 2001 – 2005, Extracted November 2006. Source file: 2006-23 APAP molecule.qry

Prescribing Specialty

For combination hydrocodone/APAP products, the general practice medicine specialty accounted for nearly a quarter of all dispensed prescriptions for these products during year 2005 (Table 6). Internal medicine followed with approximately 13% of dispensed prescriptions and dentistry followed with 12% of dispensed prescriptions. Orthopedic surgery accounted for nearly 10% of dispensed prescriptions for hydrocodone/APAP products.

For oxycodone/APAP products, the top three prescribing specialties during year 2005 were general practice medicine[7] (17%), internal medicine (12%), orthopedic surgery (9.7%), emergency medicine (7%), and dentistry (6%). Unspecified specialties accounted for approximately 7% of dispensed prescriptions for these products.

Other combination APAP products followed similar trends with these specialties appearing in among the top 10 prescribing specialties during year 2005. Interestingly, OTC single-ingredient acetaminophen products dispensed as a prescription accounted for approximately 1% of all dispensed prescriptions for APAP containing products during year 2005. Pediatricians accounted for over a quarter of those prescriptions.

Patient Age

Dispensed prescriptions for APAP containing products were analyzed for years 2002 through 2005 by patient age groups according to the following age bands: 0-5, 6-11, 12-16, 17-20, 21-30, 31-40, 41-50, 51-60, 61-70, 71 and above, and unspecified. Not surprisingly, the majority of use for prescription APAP containing products occurred in the adult population, ages 17 and above (Table 7). The codeine and combination non-injectable class (USC5 02232) was the most dispensed class of APAP containing products for all age groups except for the age 0-5 year band (see Appendix 3 for drug grouping classifications). For the 0-5 year age band, the acetaminophen class (USC5 02120) accounted for approximately 56% of dispensed prescriptions during year 2005.

Indications for use

According to a survey of approximately 3,100 office-based physician practices in the U.S., non-narcotic APAP containing products are used most frequently to treat acute pharyngitis (7.8%), general symptoms (6.7%), acute upper respiratory infection of multiple or unspecified sites (6.2%), and suppurative and unspecified otitis media (5.2%) during year 2005 (Table 8).

[7] General Practice includes general practice medicine, family practice, and doctors of osteopathy.

For the class of codeine and combination non-injectable APAP containing products, other and unspecified disorders of back (4.5%), follow-up examination (3.6%), and mononeuritis of the upper limb (2.7%) accounted for the top 3 indications associated with the use of these products during year 2005.

Co-use

For each of the top three APAP containing prescription drug classes (USC5 02120 Acetaminophen, USC4 02232 Codeine & Combination Non-Injectable, and USC 02118 Anti-migraine, combination), over 40% of these products were intended to be used in combination with another prescription drug product *to treat the same condition* during year 2005 (Table 9). When a USC 02120 product was used, oxycodone/APAP was used 1.3% of the time to treat the same condition during the year 2005.

When looking at concurrent therapy *regardless of the condition being treated*, the USC5 02120 Acetaminophen class was used in conjunction with another product in the USC5 02132 Systemic non-narcotic non-injectable class at a rate of 8.2% during year 2005 (Table 10).

DISCUSSION

Findings from this drug use analysis should be interpreted in the context of the known limitations of the databases used. The IMS Health, IMS National Sales Perspectives™ data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer to various channels of distribution. The amount of product purchased by these retail and non-retail channels of distribution may be a possible surrogate for use, if we assume that facilities purchase drugs in quantities reflective of actual patient use. Furthermore, IMS estimates that approximately 50% of all U.S. OTC sales activity is captured in this database[8].

Verispan's Physician Drug & Diagnosis Audit (PDDA) data provide estimates of patient demographics and indications for use of medicinal products in the U.S. Due to the sampling and data collection methodologies, the small sample size can make these data unstable, particularly if use is not common. Verispan recommends caution interpreting projected annual uses or mentions below 100,000 as the sample size is very small with correspondingly large confidence intervals. Furthermore, the data collected represent the intent of the prescribing physician and does not necessarily reflect what patients are doing.

The dispensed prescription data provided by Verispan's Vector One®: National database captures retail prescription activity with a reasonable amount of certainty based on the large sample size of pharmacies and data projection methodology. However, data on OTC product use is not captured in this database. A reliable estimate of OTC product usage is not possible given the limitations of the drug usage databases available at the Agency's disposal. Unlike prescription transactions which capture detailed information on the drug product being dispensed as well as patient demographic data and prescribing specialty data, transactions for OTC products are not captured in the same method. Furthermore, the ease of accessibility for OTC products compared to prescription products and the PRN (as needed) nature of use make estimating OTC product usage difficult. For these reasons, the true extent of use for OTC APAP products alone or in combination with other drug products is at best underestimated in this analysis.

CONCLUSION

The use, as measured by units sold, for prescription and OTC APAP containing products grew by 17% from year 2001 to 2005. The sale of OTC APAP products grew by 6% from year 2001 to year 2005, while the sale of prescription APAP containing products realized a growth of 38%. The majority of OTC APAP products are found in combination with other active ingredients. The most common active ingredient found in combination with APAP was pseudoephedrine. For prescription combination APAP products, hydrocodone/APAP products accounted for over 57% of all dispensed prescriptions in this market, and has been the number one dispensed prescription product in the entire market of retail dispensed prescriptions since 1997. During year 2005, the codeine and combination

[8] IMS Health, IMS National Sales Perspectives™ Retail and Non-Retail Sample Coverage of the Universe (09/15/06).

non-injectable class (USC5 02232) was the most dispensed class of APAP containing products for all age groups except for the age 0-5 year band which had the highest number of dispensed prescriptions for the acetaminophen class (USC5 02120) of products. The extent of co-use of OTC and prescription APAP products may be underestimated in this analysis due to limitations in data collection.

Appendix 1: Data Source

Outpatient Drug Usage

IMS HEALTH
IMS National Sales Perspectives™

IMS Health National Sales Perspectives™ measures the volume of drug products (both prescription and over-the-counter) and selected diagnostic products moving from manufacturers into retail and non-retail markets. The volume of drug products transferred to these markets is expressed in terms of sales dollars, vials, and market share. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings. These data are based on national projections.

VERISPAN, LLC
Vector One®: National (VONA)

Verispan's VONA is a nationally projected database which measures the retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One®database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 2 billion prescription claims yearly, representing over 160 million unique patients.

The number of dispensed prescriptions is obtained from a sample of virtually all retail pharmacies throughout the U.S and represents approximately half of the retail prescriptions dispensed nationwide. Verispan receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores. Mail order prescriptions are not included in the sample at this time.

VERISPAN, LLC
Physician Drug & Diagnosis Audit (PDDA)

Verispan's Physician Drug & Diagnosis Audit (PDDA) is a monthly survey that monitors disease states and the physician intended prescribing habits on a national-level. The survey is designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The audit is composed of approximately 3,100 office-based physicians representing 29 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

The term drug uses refers to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a drug use does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

Appendix 2: Uniform System of Classification (USC5) groupings for OTC combination APAP products by active ingredients[9]

34500 NON-NARC COUGH COMB W/O EXPECTORANT:
ACETAMINOPHEN
DEXTROMETHORPHAN
PSEUDOEPHEDRINE
DOXYLAMINE
CHLORPHENIRAMINE
PHENYLEPHRINE
DIPHENHYDRAMINE
BROMPHENIRAMINE
PYRILAMINE
GUAIFENESIN
CAFFEINE
PHENYLPROPANOLAMINE

02100 ANALG NON-NARCOTIC:
ACETAMINOPHEN
DIPHENHYDRAMINE
CAFFEINE
ACETYLSALICYLIC ACID
PHENYLTOLOXAMINE
CITRIC ACID
SODIUM
PAMABROM
PHENYLEPHRINE
SALICYLAMIDE
MELATONIN
CALCIUM
MAGNESIUM

14300 COMB W/O EXPECTORANT:
ACETAMINOPHEN
PSEUDOEPHEDRINE
CHLORPHENIRAMINE
PHENYLEPHRINE
DIPHENHYDRAMINE
DOXYLAMINE
BROMPHENIRAMINE
PHENYLPROPANOLAMINE
DEXTROMETHORPHAN
CLEMASTINE
DEXBROMPHENIRAMINE
ATROPINE
PHENYLTOLOXAMINE
TRIPROLIDINE
SALICYLAMIDE
CAFFEINE
EPHEDRINE

34600 NON-NARCOTIC COUGH COMB W/EXPECTORANT:
ACETAMINOPHEN
DEXTROMETHORPHAN
PSEUDOEPHEDRINE
GUAIFENESIN
PHENYLEPHRINE
PHENYLPROPANOLAMINE

78800 MISCELLANEOUS, OTHER:
ACETAMINOPHEN
PAMABROM
PYRILAMINE
CAFFEINE
PSEUDOEPHEDRINE
PYRIDOXINE

14500 COMBINATION W/EXPECTORANT:
ACETAMINOPHEN
GUAIFENESIN
PSEUDOEPHEDRINE
CAFFEINE
PHENYLEPHRINE

09100 ANTIARTHRITIC, SYSTEMIC:
ACETAMINOPHEN
CAFFEINE
MAGNESIUM

05100 ANTACIDS, PLAIN:
CITRIC ACID
ACETAMINOPHEN
SODIUM

67200 NON-BARBITURATE:
ACETAMINOPHEN
DIPHENHYDRAMINE

28200 RESPIRATORY NSAID:
ACETAMINOPHEN
PSEUDOEPHEDRINE
CROMOLYN

[9] IMS Health, IMS Natinoal Sales Perspectives™: Retail and Non-Retail, Year 2005, Extracted November 2006; Source file: 0611apa4.dvr

Appendix 3: Uniform System of Classification (USC5) drug groupings for prescription APAP containing products[10].

02232 CODEINE & COMB NON-INJ
- hydrocodone bitartrate/apap
- oxycodone hcl/acetaminophen
- codeine phosphate/apap
- codeine/apap/caffein/butalb
- hydrocodone bit/acetaminophen
- hydrocodone bitrate/apap
- hydrocodone/apap/caffein/butal
- codeine/apap/phenyltolox
- codeine phosphate/apap/butalb

02212 PROPOXYPHENES
- propoxyphene napsylate/apap
- propoxyphene/napsylate/apap
- propoxyphene hcl/acetaminophen
- propoxyphene/acetaminophen

02120 ACETAMINOPHEN
- acetaminophen/caffeine/butalb
- acetaminophen
- acetaminophen/butalbital
- acetaminophen/phenyltolox
- acetaminophen/dp-hydramine
- phenyltoloxamine/apap

02132 SYN NON-NARC NON-INJ
- tramadol hcl/acetaminophen
- acetaminophen/pentazocine

02118 ANTI-MIGRAINE,COMB
- apap/isometheptene/dichlphen
- acetaminophen/caffeine/isometh

02150 SYN NON-NARCOTIC COMBO
- acetaminophen/caffeine/butalb
- acetaminophen/phenyltolx cit
- acetaminophen/phenyltolox
- asa/sal-amide/apap/caffein
- acetaminophen/phenyltolx
- acetaminophen/phenyl tolx cit
- acetaminophen/dp-hydramine

34110 COLD W/ANALGESICS
- acetaminophen/chlorphenir
- phenylpropanolamine hcl/apap

79100 PTY PREMNST TENS
- acetaminophen/pyrilamine

[10] Verispan, VONA: Years 2001 – 2005, Extracted November 2006. Source file: 2006-23 APAP class molecule.qry

Appendix 4: Tables and Figures

Table 6: Total number of dispensed prescriptions (in thousands) for APAP containing products by prescribing specialty, Years 2001 - 2005

	2001		2002		2003		2004		2005	
	TRxs (000)	*Share %*	TRxs (000)	*Share %*	TRxs (000)	*Share %*	TRxs (000)	*Share %*	TRxs (000)	*Share %*
TOTAL MARKET	161,154	*100.0%*	165,578	*100.0%*	169,692	*100.0%*	174,496	*100.0%*	182,287	*100.0%*
hydrocodone/APAP	80,492	*49.9%*	86,081	*52.0%*	90,890	*53.6%*	96,571	*55.3%*	104,199	*57.2%*
GP/FM/DO	18,437	*22.9%*	18,657	*21.7%*	20,304	*22.3%*	21,677	*22.4%*	24,305	*23.3%*
IM	10,290	*12.8%*	10,657	*12.4%*	11,603	*12.8%*	12,380	*12.8%*	13,817	*13.3%*
DENT	10,849	*13.5%*	11,342	*13.2%*	11,541	*12.7%*	11,894	*12.3%*	12,522	*12.0%*
ORTH SURG	9,571	*11.9%*	8,974	*10.4%*	9,360	*10.3%*	9,427	*9.8%*	9,979	*9.6%*
UNSPEC	672	*0.8%*	6,667	*7.7%*	6,282	*6.9%*	7,838	*8.1%*	7,308	*7.0%*
EM	6,188	*7.7%*	5,770	*6.7%*	6,001	*6.6%*	6,035	*6.2%*	6,270	*6.0%*
GEN SURG	3,083	*3.8%*	2,982	*3.5%*	3,048	*3.4%*	3,090	*3.2%*	3,184	*3.1%*
ANES	1,857	*2.3%*	1,919	*2.2%*	2,108	*2.3%*	2,268	*2.3%*	2,501	*2.4%*
PA	910	*1.1%*	971	*1.1%*	1,272	*1.4%*	1,688	*1.7%*	2,261	*2.2%*
OB/GYN	2,238	*2.8%*	2,252	*2.6%*	2,266	*2.5%*	2,198	*2.3%*	2,222	*2.1%*
All Others	16,397	*20.4%*	15,891	*18.5%*	17,105	*18.8%*	18,076	*18.7%*	19,830	*19.0%*
oxycodone hcl/APAP	16,724	*10.4%*	18,025	*10.9%*	19,835	*11.7%*	21,728	*12.5%*	24,022	*13.2%*
GP/FM/DO	2,491	*14.9%*	2,667	*14.8%*	3,097	*15.6%*	3,520	*16.2%*	4,105	*17.1%*
IM	2,007	*12.0%*	2,061	*11.4%*	2,357	*11.9%*	2,584	*11.9%*	2,945	*12.3%*
ORTH SURG	1,828	*10.9%*	1,826	*10.1%*	2,007	*10.1%*	2,122	*9.8%*	2,341	*9.7%*
UNSPEC	124	*0.7%*	1,586	*8.8%*	1,566	*7.9%*	1,887	*8.7%*	1,754	*7.3%*
EM	1,334	*8.0%*	1,245	*6.9%*	1,393	*7.0%*	1,523	*7.0%*	1,743	*7.3%*
DENT	1,354	*8.1%*	1,351	*7.5%*	1,374	*6.9%*	1,405	*6.5%*	1,500	*6.2%*
OB/GYN	1,202	*7.2%*	1,134	*6.3%*	1,167	*5.9%*	1,159	*5.3%*	1,229	*5.1%*
GEN SURG	1,031	*6.2%*	959	*5.3%*	989	*5.0%*	998	*4.6%*	1,041	*4.3%*
AO SURG	720	*4.3%*	695	*3.9%*	733	*3.7%*	765	*3.5%*	823	*3.4%*
ANES	421	*2.5%*	498	*2.8%*	608	*3.1%*	707	*3.3%*	819	*3.4%*
All Others	4,212	*25.2%*	4,004	*22.2%*	4,543	*22.9%*	5,059	*23.3%*	5,724	*23.8%*
propoxyphene nap/APAP	27,603	*17.1%*	25,859	*15.6%*	24,924	*14.7%*	23,916	*13.7%*	23,073	*12.7%*
GP/FM/DO	8,016	*29.0%*	7,010	*27.1%*	6,755	*27.1%*	6,359	*26.6%*	6,310	*27.3%*
IM	5,488	*19.9%*	4,939	*19.1%*	4,830	*19.4%*	4,582	*19.2%*	4,524	*19.6%*
ORTH SURG	2,836	*10.3%*	2,346	*9.1%*	2,291	*9.2%*	2,124	*8.9%*	2,018	*8.7%*
UNSPEC	207	*0.7%*	1,985	*7.7%*	1,662	*6.7%*	1,839	*7.7%*	1,526	*6.6%*
DENT	1,373	*5.0%*	1,319	*5.1%*	1,323	*5.3%*	1,312	*5.5%*	1,266	*5.5%*
OB/GYN	1,149	*4.2%*	982	*3.8%*	938	*3.8%*	867	*3.6%*	783	*3.4%*
EM	1,089	*3.9%*	844	*3.3%*	813	*3.3%*	788	*3.3%*	760	*3.3%*
GEN SURG	1,141	*4.1%*	947	*3.7%*	885	*3.5%*	817	*3.4%*	737	*3.2%*
AO SURG	723	*2.6%*	634	*2.5%*	625	*2.5%*	598	*2.5%*	563	*2.4%*
RHEUM	634	*2.3%*	584	*2.3%*	581	*2.3%*	543	*2.3%*	539	*2.3%*
All Others	4,945	*17.9%*	4,268	*16.5%*	4,221	*16.9%*	4,086	*17.1%*	4,047	*17.5%*
codeine/APAP	22,127	*13.7%*	19,834	*12.0%*	18,203	*10.7%*	16,913	*9.7%*	15,924	*8.7%*
GP/FM/DO	4,781	*21.6%*	3,799	*19.2%*	3,450	*19.0%*	3,127	*18.5%*	3,058	*19.2%*
DENT	3,831	*17.3%*	3,547	*17.9%*	3,278	*18.0%*	3,047	*18.0%*	2,824	*17.7%*
IM	3,255	*14.7%*	2,614	*13.2%*	2,381	*13.1%*	2,150	*12.7%*	2,072	*13.0%*
UNSPEC	187	*0.8%*	1,946	*9.8%*	1,715	*9.4%*	1,830	*10.8%*	1,532	*9.6%*
EM	1,327	*6.0%*	985	*5.0%*	914	*5.0%*	818	*4.8%*	773	*4.9%*
ORTH SURG	1,260	*5.7%*	964	*4.9%*	865	*4.8%*	757	*4.5%*	693	*4.4%*
OB/GYN	1,127	*5.1%*	897	*4.5%*	823	*4.5%*	738	*4.4%*	652	*4.1%*
ENT	691	*3.1%*	667	*3.4%*	630	*3.5%*	572	*3.4%*	543	*3.4%*
PED	647	*2.9%*	571	*2.9%*	560	*3.1%*	530	*3.1%*	520	*3.3%*
HOSP	783	*3.5%*	413	*2.1%*	405	*2.2%*	391	*2.3%*	380	*2.4%*
All Others	4,239	*19.2%*	3,430	*17.3%*	3,182	*17.5%*	2,952	*17.5%*	2,877	*18.1%*

Verispan, VONA, Years 2001 - 2005, Extracted November 2006; Source file: 2006-23 APAP molecule MD.qry

Table 6 continued on next page.

Table 6, continued: Total number of dispensed prescriptions (in thousands) for APAP containing products by prescribing specialty, Years 2001 - 2005

	2001		2002		2003		2004		2005	
	TRxs (000)	*Share* %	TRxs (000)	*Share* %	TRxs (000)	*Share* %	TRxs (000)	*Share* %	TRxs (000)	*Share* %
tramadol hcl/APAP	377	*0.2%*	4,000	*2.4%*	4,973	*2.9%*	5,337	*3.1%*	5,509	*3.0%*
GP/FM/DO	129	*34.1%*	1,154	*28.8%*	1,404	*28.2%*	1,501	*28.1%*	1,577	*28.6%*
IM	77	*20.4%*	758	*18.9%*	959	*19.3%*	1,059	*19.9%*	1,179	*21.4%*
ORTH SURG	51	*13.6%*	516	*12.9%*	625	*12.6%*	607	*11.4%*	578	*10.5%*
UNSPEC	4	*1.2%*	396	*9.9%*	459	*9.2%*	556	*10.4%*	490	*8.9%*
RHEUM	18	*4.8%*	194	*4.9%*	223	*4.5%*	220	*4.1%*	220	*4.0%*
ANES	12	*3.1%*	129	*3.2%*	160	*3.2%*	172	*3.2%*	166	*3.0%*
EM	15	*4.1%*	132	*3.3%*	162	*3.3%*	158	*3.0%*	154	*2.8%*
PM&R	11	*2.9%*	113	*2.8%*	148	*3.0%*	146	*2.7%*	150	*2.7%*
PA	7	*1.9%*	56	*1.4%*	81	*1.6%*	104	*2.0%*	122	*2.2%*
NP	5	*1.2%*	43	*1.1%*	68	*1.4%*	89	*1.7%*	109	*2.0%*
All Others	47	*12.5%*	510	*12.7%*	683	*13.7%*	724	*13.6%*	763	*13.9%*
APAP/caffeine/butalb	5,841	*3.6%*	5,410	*3.3%*	5,180	*3.1%*	5,103	*2.9%*	4,738	*2.6%*
GP/FM/DO	2,214	*37.9%*	1,872	*34.6%*	1,766	*34.1%*	1,704	*33.4%*	1,603	*33.8%*
IM	1,495	*25.6%*	1,299	*24.0%*	1,280	*24.7%*	1,251	*24.5%*	1,173	*24.8%*
UNSPEC	54	*0.9%*	494	*9.1%*	422	*8.1%*	468	*9.2%*	378	*8.0%*
NEURO	490	*8.4%*	419	*7.7%*	404	*7.8%*	395	*7.7%*	376	*7.9%*
OB/GYN	283	*4.8%*	244	*4.5%*	233	*4.5%*	228	*4.5%*	209	*4.4%*
NP	80	*1.4%*	74	*1.4%*	87	*1.7%*	96	*1.9%*	102	*2.2%*
EM	122	*2.1%*	105	*1.9%*	103	*2.0%*	104	*2.0%*	101	*2.1%*
PA	71	*1.2%*	56	*1.0%*	63	*1.2%*	71	*1.4%*	74	*1.6%*
PED	81	*1.4%*	74	*1.4%*	72	*1.4%*	70	*1.4%*	65	*1.4%*
PSYCH	90	*1.5%*	68	*1.2%*	65	*1.3%*	63	*1.2%*	56	*1.2%*
All Others	861	*14.7%*	705	*13.0%*	685	*13.2%*	653	*12.8%*	600	*12.7%*
acetaminophen	3,988	*2.5%*	2,856	*1.7%*	2,670	*1.6%*	2,014	*1.2%*	2,202	*1.2%*
PED	1,143	*28.7%*	776	*27.2%*	708	*26.5%*	498	*24.7%*	597	*27.1%*
UNSPEC	64	*1.6%*	563	*19.7%*	684	*25.6%*	596	*29.6%*	558	*25.3%*
GP/FM/DO	1,152	*28.9%*	690	*24.2%*	566	*21.2%*	410	*20.3%*	468	*21.3%*
IM	671	*16.8%*	287	*10.1%*	246	*9.2%*	191	*9.5%*	231	*10.5%*
HOSP	239	*6.0%*	99	*3.5%*	83	*3.1%*	59	*2.9%*	59	*2.7%*
EM	105	*2.6%*	65	*2.3%*	64	*2.4%*	42	*2.1%*	48	*2.2%*
NP	66	*1.7%*	49	*1.7%*	42	*1.6%*	30	*1.5%*	38	*1.7%*
PA	48	*1.2%*	18	*0.6%*	23	*0.9%*	18	*0.9%*	28	*1.3%*
DENT	45	*1.1%*	43	*1.5%*	36	*1.4%*	25	*1.3%*	27	*1.2%*
OB/GYN	45	*1.1%*	29	*1.0%*	25	*0.9%*	17	*0.8%*	20	*0.9%*
All Others	410	*10.3%*	237	*8.3%*	192	*7.2%*	129	*6.4%*	128	*5.8%*
All Others	4,003	*2.5%*	3,513	*2.1%*	3,016	*1.8%*	2,912	*1.7%*	2,619	*1.4%*

Verispan, VONA, Years 2001 - 2005, Extracted November 2006; Source file: 2006-23 APAP molecule MD.qry

Table 7: Total number of dispensed prescriptions (in thousands) for APAP containing products by patient age, Years 2002 - 2005

	2002		2003		2004		2005	
	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*
	(000)	*%*	(000)	*%*	(000)	*%*	(000)	*%*
TOTAL MARKET	165,594	*100.0%*	169,696	*100.0%*	174,496	*100.0%*	182,287	*100.0%*
0-5	2,426	*1.5%*	2,276	*1.3%*	1,922	*1.1%*	1,978	*1.1%*
02120 ACETAMINOPHEN	1,412	*58.2%*	1,291	*56.7%*	1,002	*52.1%*	1,107	*56.0%*
02232 CODEINE & COMB NON-INJ	990	*40.8%*	967	*42.5%*	906	*47.2%*	860	*43.5%*
02212 PROPOXYPHENES	18	*0.8%*	14	*0.6%*	10	*0.5%*	8	*0.4%*
02132 SYN NON-NARC NON-INJ	5	*0.2%*	4	*0.2%*	3	*0.2%*	3	*0.1%*
02118 ANTI-MIGRAINE,COMB	1	*0.0%*	1	*0.0%*	0	*0.0%*	0	*0.0%*
02150 SYN NON-NARC COMBO	--	--	0	*0.0%*	0	*0.0%*	0	*0.0%*
34110 COLD W/ANALGESICS	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*
6-11	1,835	*1.1%*	1,819	*1.1%*	1,569	*0.9%*	1,582	*0.9%*
02232 CODEINE & COMB NON-INJ	1,380	*75.2%*	1,364	*75.0%*	1,251	*79.7%*	1,219	*77.1%*
02120 ACETAMINOPHEN	420	*22.9%*	421	*23.2%*	289	*18.4%*	338	*21.3%*
02212 PROPOXYPHENES	22	*1.2%*	20	*1.1%*	17	*1.1%*	15	*0.9%*
02118 ANTI-MIGRAINE,COMB	12	*0.6%*	11	*0.6%*	10	*0.6%*	7	*0.4%*
02132 SYN NON-NARC NON-INJ	2	*0.1%*	3	*0.1%*	2	*0.1%*	3	*0.2%*
02150 SYN NON-NARC COMBO	--	--	0	*0.0%*	1	*0.1%*	1	*0.1%*
34110 COLD W/ANALGESICS	--	--	0	*0.0%*	0	*0.0%*	0	*0.0%*
12-16	2,695	*1.6%*	2,688	*1.6%*	2,568	*1.5%*	2,527	*1.4%*
02232 CODEINE & COMB NON-INJ	2,216	*82.2%*	2,220	*82.6%*	2,171	*84.5%*	2,152	*85.2%*
02212 PROPOXYPHENES	209	*7.8%*	198	*7.4%*	182	*7.1%*	164	*6.5%*
02120 ACETAMINOPHEN	177	*6.6%*	184	*6.8%*	133	*5.2%*	138	*5.5%*
02118 ANTI-MIGRAINE,COMB	71	*2.6%*	60	*2.2%*	55	*2.2%*	47	*1.8%*
02132 SYN NON-NARC NON-INJ	21	*0.8%*	26	*1.0%*	25	*1.0%*	23	*0.9%*
02150 SYN NON-NARC COMBO	--	--	0	*0.0%*	2	*0.1%*	3	*0.1%*
34110 COLD W/ANALGESICS	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*
17-20	4,920	*3.0%*	4,889	*2.9%*	4,818	*2.8%*	4,848	*2.7%*
02232 CODEINE & COMB NON-INJ	4,115	*83.6%*	4,145	*84.8%*	4,136	*85.8%*	4,221	*87.1%*
02212 PROPOXYPHENES	485	*9.9%*	442	*9.0%*	410	*8.5%*	375	*7.7%*
02120 ACETAMINOPHEN	156	*3.2%*	143	*2.9%*	119	*2.5%*	113	*2.3%*
02132 SYN NON-NARC NON-INJ	70	*1.4%*	81	*1.7%*	79	*1.6%*	75	*1.5%*
02118 ANTI-MIGRAINE,COMB	94	*1.9%*	78	*1.6%*	72	*1.5%*	62	*1.3%*
02150 SYN NON-NARC COMBO	--	--	0	*0.0%*	1	*0.0%*	3	*0.1%*
34110 COLD W/ANALGESICS	--	--	--	--	0	*0.0%*	0	*0.0%*
21-30	17,635	*10.6%*	17,861	*10.5%*	18,214	*10.4%*	18,468	*10.1%*
02232 CODEINE & COMB NON-INJ	14,577	*82.7%*	15,013	*84.1%*	15,549	*85.4%*	16,026	*86.8%*
02212 PROPOXYPHENES	1,834	*10.4%*	1,686	*9.4%*	1,580	*8.7%*	1,440	*7.8%*
02120 ACETAMINOPHEN	596	*3.4%*	534	*3.0%*	480	*2.6%*	443	*2.4%*
02132 SYN NON-NARC NON-INJ	335	*1.9%*	384	*2.1%*	378	*2.1%*	362	*2.0%*
02118 ANTI-MIGRAINE,COMB	293	*1.7%*	244	*1.4%*	223	*1.2%*	186	*1.0%*
02150 SYN NON-NARC COMBO	--	--	1	*0.0%*	5	*0.0%*	10	*0.1%*
34110 COLD W/ANALGESICS	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*

Verispan, VONA, Years 2002 - 2005, Extracted November 2006; Source file: 2006-23 APAP Age Class.qry

Table 7 continued on next page.

Table 7, continued: Total number of dispensed prescriptions (in thousands) for APAP containing products by patient age, Years 2002 - 2005

	2002		2003		2004		2005	
	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*
	(000)	*%*	(000)	*%*	(000)	*%*	(000)	*%*
31-40	29,002	*17.5%*	28,432	*16.8%*	27,835	*16.0%*	27,303	*15.0%*
02232 CODEINE & COMB NON-INJ	23,356	*80.5%*	23,254	*81.8%*	23,110	*83.0%*	23,137	*84.7%*
02212 PROPOXYPHENES	3,220	*11.1%*	2,896	*10.2%*	2,615	*9.4%*	2,300	*8.4%*
02120 ACETAMINOPHEN	1,289	*4.4%*	1,149	*4.0%*	1,031	*3.7%*	889	*3.3%*
02132 SYN NON-NARC NON-INJ	679	*2.3%*	753	*2.6%*	728	*2.6%*	670	*2.5%*
02118 ANTI-MIGRAINE,COMB	459	*1.6%*	378	*1.3%*	344	*1.2%*	289	*1.1%*
02150 SYN NON-NARC COMBO	--	--	2	*0.0%*	8	*0.0%*	18	*0.1%*
34110 COLD W/ANALGESICS	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*
41-50	38,417	*23.2%*	39,368	*23.2%*	40,145	*23.0%*	41,168	*22.6%*
02232 CODEINE & COMB NON-INJ	30,049	*78.2%*	31,338	*79.6%*	32,548	*81.1%*	34,164	*83.0%*
02212 PROPOXYPHENES	4,891	*12.7%*	4,581	*11.6%*	4,273	*10.6%*	3,924	*9.5%*
02120 ACETAMINOPHEN	1,961	*5.1%*	1,837	*4.7%*	1,727	*4.3%*	1,553	*3.8%*
02132 SYN NON-NARC NON-INJ	977	*2.5%*	1,161	*2.9%*	1,173	*2.9%*	1,145	*2.8%*
02118 ANTI-MIGRAINE,COMB	539	*1.4%*	450	*1.1%*	416	*1.0%*	361	*0.9%*
02150 SYN NON-NARC COMBO	--	--	1	*0.0%*	8	*0.0%*	20	*0.0%*
34110 COLD W/ANALGESICS	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*
51-60	28,660	*17.3%*	30,433	*17.9%*	32,269	*18.5%*	35,205	*19.3%*
02232 CODEINE & COMB NON-INJ	21,364	*74.5%*	23,054	*75.8%*	24,991	*77.4%*	28,043	*79.7%*
02212 PROPOXYPHENES	4,769	*16.6%*	4,696	*15.4%*	4,520	*14.0%*	4,410	*12.5%*
02120 ACETAMINOPHEN	1,399	*4.9%*	1,385	*4.6%*	1,372	*4.3%*	1,320	*3.7%*
02132 SYN NON-NARC NON-INJ	803	*2.8%*	1,015	*3.3%*	1,108	*3.4%*	1,171	*3.3%*
02118 ANTI-MIGRAINE,COMB	325	*1.1%*	283	*0.9%*	272	*0.8%*	248	*0.7%*
02150 SYN NON-NARC COMBO	--	--	1	*0.0%*	5	*0.0%*	13	*0.0%*
34110 COLD W/ANALGESICS	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*
61-70	17,535	*10.6%*	18,580	*10.9%*	19,928	*11.4%*	21,886	*12.0%*
02232 CODEINE & COMB NON-INJ	12,308	*70.2%*	13,253	*71.3%*	14,540	*73.0%*	16,408	*75.0%*
02212 PROPOXYPHENES	3,926	*22.4%*	3,896	*21.0%*	3,864	*19.4%*	3,887	*17.8%*
02132 SYN NON-NARC NON-INJ	512	*2.9%*	662	*3.6%*	757	*3.8%*	827	*3.8%*
02120 ACETAMINOPHEN	679	*3.9%*	673	*3.6%*	668	*3.4%*	665	*3.0%*
02118 ANTI-MIGRAINE,COMB	111	*0.6%*	97	*0.5%*	97	*0.5%*	94	*0.4%*
02150 SYN NON-NARC COMBO	--	--	0	*0.0%*	2	*0.0%*	6	*0.0%*
34110 COLD W/ANALGESICS	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*
71+	21,415	*12.9%*	22,278	*13.1%*	23,551	*13.5%*	25,725	*14.1%*
02232 CODEINE & COMB NON-INJ	13,172	*61.5%*	13,901	*62.4%*	15,075	*64.0%*	17,046	*66.3%*
02212 PROPOXYPHENES	6,704	*31.3%*	6,646	*29.8%*	6,605	*28.0%*	6,667	*25.9%*
02132 SYN NON-NARC NON-INJ	757	*3.5%*	996	*4.5%*	1,153	*4.9%*	1,291	*5.0%*
02120 ACETAMINOPHEN	726	*3.4%*	683	*3.1%*	663	*2.8%*	668	*2.6%*
02118 ANTI-MIGRAINE,COMB	56	*0.3%*	52	*0.2%*	52	*0.2%*	49	*0.2%*
02150 SYN NON-NARC COMBO	--	--	0	*0.0%*	1	*0.0%*	5	*0.0%*
34110 COLD W/ANALGESICS	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*
UNSPEC.	1,053	*0.6%*	1,072	*0.6%*	1,676	*1.0%*	1,596	*0.9%*
02232 CODEINE & COMB NON-INJ	820	*77.9%*	823	*76.7%*	1,333	*79.5%*	1,283	*80.4%*
02212 PROPOXYPHENES	144	*13.7%*	153	*14.2%*	209	*12.5%*	200	*12.5%*
02120 ACETAMINOPHEN	61	*5.8%*	62	*5.8%*	83	*4.9%*	64	*4.0%*
02132 SYN NON-NARC NON-INJ	24	*2.2%*	32	*3.0%*	48	*2.8%*	46	*2.9%*
02118 ANTI-MIGRAINE,COMB	4	*0.4%*	3	*0.2%*	3	*0.2%*	2	*0.1%*
02150 SYN NON-NARC COMBO	--	--	0	*0.0%*	0	*0.0%*	1	*0.0%*
34110 COLD W/ANALGESICS	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*

Verispan, VONA, Years 2002 - 2005, Extracted November 2006; Source file: 2006-23 APAP Age Class.qry

Table 8: Top 10 diagnoses associated with the use of APAP containing drug products as reported by office-based physician practices , Years 2001 - 2005

	2001		2002		2003		2004		2005	
	Uses (000)	*Share* %	Uses (000)	*Share* %	Uses (000)	*Share* %	Uses (000)	*Share* %	Uses (000)	*Share* %
TOTAL MARKET	32,598	*100.0%*	33,663	*100.0%*	35,099	*100.0%*	33,011	*100.0%*	34,053	*100.0%*
02120 ACETAMINOPHEN	20,559	*63.1%*	21,907	*65.1%*	23,447	*66.8%*	22,053	*66.8%*	24,416	*71.7%*
462 ACUTE PHARYNGITIS	1,407	*6.8%*	1,602	*7.3%*	1,678	*7.2%*	1,488	*6.7%*	1,913	*7.8%*
780 GENERAL SYMPTOMS	1,208	*5.9%*	1,304	*6.0%*	1,480	*6.3%*	1,420	*6.4%*	1,671	*6.7%*
465 AC URI MULT SITES/NOS	1,520	*7.4%*	1,535	*7.0%*	1,622	*6.9%*	1,434	*6.5%*	1,518	*6.2%*
382 OTITIS MEDIA, SUPPUR/NOS	1,086	*5.3%*	1,276	*5.8%*	1,357	*5.8%*	1,077	*4.9%*	1,261	*5.2%*
V20 HEALTH SUPERVISION CHILD	740	*3.6%*	790	*3.6%*	1,244	*5.3%*	1,105	*5.0%*	1,114	*4.6%*
079 VIRAL INF IN OTH DIS/NOS	858	*4.2%*	1,090	*5.0%*	1,121	*4.8%*	878	*4.0%*	1,018	*4.2%*
784 SYMPTOMS INVOL HEAD/NECK	1,261	*6.1%*	1,123	*5.1%*	1,019	*4.3%*	1,064	*4.8%*	1,010	*4.1%*
715 OSTEOARTHROSIS ET AL	582	*2.8%*	578	*2.6%*	610	*2.6%*	647	*2.9%*	904	*3.7%*
724 BACK DISORDER NEC & NOS	436	*2.1%*	473	*2.2%*	486	*2.1%*	582	*2.6%*	716	*2.9%*
034 STREP THROAT/SCARLET FEV	349	*1.7%*	417	*1.9%*	508	*2.2%*	558	*2.5%*	566	*2.3%*
All Others	11,113	*54.1%*	11,720	*53.5%*	12,322	*52.6%*	11,802	*53.5%*	12,726	*52.1%*
02232 CODEINE & COMB NON-INJ	10,963	*33.6%*	10,771	*32.0%*	10,796	*30.8%*	10,047	*30.4%*	8,751	*25.7%*
724 BACK DISORDER NEC & NOS	751	*6.9%*	596	*5.5%*	657	*6.1%*	645	*6.4%*	395	*4.5%*
V67 FOLLOW-UP EXAMINATION	493	*4.5%*	459	*4.3%*	525	*4.9%*	417	*4.2%*	311	*3.6%*
354 MONONEURITIS UPPER LIMB	141	*1.3%*	160	*1.5%*	215	*2.0%*	240	*2.4%*	238	*2.7%*
813 RADIUS & ULNA FRACTURE	253	*2.3%*	244	*2.3%*	348	*3.2%*	176	*1.7%*	233	*2.7%*
845 SPRAIN OF ANKLE & FOOT	204	*1.9%*	251	*2.3%*	185	*1.7%*	123	*1.2%*	225	*2.6%*
382 OTITIS MEDIA, SUPPUR/NOS	195	*1.8%*	224	*2.1%*	133	*1.2%*	162	*1.6%*	191	*2.2%*
847 SPRAIN OF BACK NEC/NOS	255	*2.3%*	311	*2.9%*	287	*2.7%*	242	*2.4%*	177	*2.0%*
784 SYMPTOMS INVOL HEAD/NECK	209	*1.9%*	260	*2.4%*	194	*1.8%*	241	*2.4%*	164	*1.9%*
729 OTHER SOFT TISSUE DIS	159	*1.4%*	120	*1.1%*	101	*0.9%*	168	*1.7%*	164	*1.9%*
816 FRACTURE PHALANGES, HAND	108	*1.0%*	137	*1.3%*	104	*1.0%*	109	*1.1%*	155	*1.8%*
All Others	8,195	*74.8%*	8,010	*74.4%*	8,046	*74.5%*	7,525	*74.9%*	6,498	*74.2%*
02118 ANTI-MIGRAINE,COMB	831	*2.6%*	684	*2.0%*	662	*1.9%*	559	*1.7%*	577	*1.7%*
346 MIGRAINE	362	*43.6%*	254	*37.1%*	280	*42.2%*	213	*38.1%*	255	*44.2%*
784 SYMPTOMS INVOL HEAD/NECK	355	*42.7%*	354	*51.7%*	277	*41.8%*	259	*46.4%*	186	*32.3%*
307 SPECIAL SYMPTOM NEC	75	*9.0%*	50	*7.3%*	100	*15.1%*	78	*13.9%*	100	*17.3%*
368 VISUAL DISTURBANCES	--	--	--	--	--	--	--	--	10	*1.7%*
625 FEMALE GENITAL SYMPTOMS	5	*0.6%*	--	--	--	--	--	--	7	*1.2%*
401 ESSENTIAL HYPERTENSION	--	--	--	--	--	--	--	--	6	*1.1%*
311 DEPRESSIVE DISORDER NEC	--	--	--	--	--	--	--	--	6	*1.0%*
435 TRANSIENT CEREB ISCHEMIA	--	--	--	--	--	--	--	--	5	*0.8%*
322 MENINGITIS, UNSPECIFIED	--	--	--	--	--	--	--	--	3	*0.5%*
385 DIS MID EAR/MASTOID NEC	2	*0.2%*	--	--	--	--	--	--	--	--
All Others	33	*3.9%*	26	*3.8%*	6	*0.9%*	9	*1.6%*	--	--
All Others	245	*0.8%*	302	*0.9%*	194	*0.6%*	352	*1.1%*	308	*0.9%*

Verispan, PDDA: Years 2001 - 2005, Extracted November 2006; Source file: PDDA 2006-23 APAP class Dx3.qry

Table 9: Total occurrences of *concomittant* drug use for the USC classes of APAP containing drug products, Years 2001 - 2005

	2001		2002		2003		2004		2005	
	Occur	*Share*	Occur	*Share*	Occur	*Share*	Occur	*Share*	Occur	*Share*
	(000)	*%*	(000)	*%*	(000)	*%*	(000)	*%*	(000)	*%*
TOTAL MARKET	30,315	*100.0%*	31,121	*100.0%*	32,094	*100.0%*	30,359	*100.0%*	31,249	*100.0%*
02120 ACETAMINOPHEN	19,127	*63.1%*	20,095	*64.6%*	21,290	*66.3%*	20,143	*66.3%*	22,254	*71.2%*
Used Alone	10,519	*55.0%*	11,296	*56.2%*	11,025	*51.8%*	10,639	*52.8%*	11,915	*53.5%*
ibuprofen	1,615	*8.4%*	1,824	*9.1%*	2,559	*12.0%*	2,074	*10.3%*	2,310	*10.4%*
amoxicillin trihydrate	1,741	*9.1%*	1,660	*8.3%*	1,644	*7.7%*	1,574	*7.8%*	1,715	*7.7%*
azithromycin	349	*1.8%*	573	*2.9%*	744	*3.5%*	683	*3.4%*	705	*3.2%*
pneumococc 7-val conj-dip crm	142	*0.7%*	208	*1.0%*	453	*2.1%*	428	*2.1%*	486	*2.2%*
diphth/tetanus/pertussis	167	*0.9%*	331	*1.6%*	326	*1.5%*	413	*2.1%*	391	*1.8%*
amoxicillin/clavulanate	423	*2.2%*	576	*2.9%*	532	*2.5%*	438	*2.2%*	379	*1.7%*
cefdinir	58	*0.3%*	119	*0.6%*	235	*1.1%*	229	*1.1%*	344	*1.5%*
poliomyelitis vaccine	157	*0.8%*	203	*1.0%*	341	*1.6%*	329	*1.6%*	335	*1.5%*
oxycodone hcl/acetaminophen	71	*0.4%*	191	*1.0%*	360	*1.7%*	151	*0.8%*	291	*1.3%*
haemophilus b vaccine	121	*0.6%*	165	*0.8%*	421	*2.0%*	286	*1.4%*	277	*1.2%*
benzocaine	104	*0.5%*	161	*0.8%*	181	*0.9%*	120	*0.6%*	271	*1.2%*
thimerosal/boric acid	180	*0.9%*	195	*1.0%*	200	*0.9%*	266	*1.3%*	239	*1.1%*
cyclobenzaprine hcl	101	*0.5%*	84	*0.4%*	97	*0.5%*	181	*0.9%*	237	*1.1%*
hep b vaccine/dp (a) t-polio	--	--	--	--	89	*0.4%*	149	*0.7%*	226	*1.0%*
All Others	8,884	*46.4%*	9,405	*46.8%*	11,139	*52.3%*	9,999	*49.6%*	11,537	*51.8%*
02232 CODEINE & COMB NON-INJ	10,164	*33.5%*	10,078	*32.4%*	9,979	*31.1%*	9,361	*30.8%*	8,185	*26.2%*
Used Alone	6,037	*59.4%*	5,736	*56.9%*	5,906	*59.2%*	5,363	*57.3%*	4,782	*58.4%*
ibuprofen	520	*5.1%*	474	*4.7%*	481	*4.8%*	535	*5.7%*	555	*6.8%*
cephalexin	572	*5.6%*	597	*5.9%*	792	*7.9%*	715	*7.6%*	505	*6.2%*
cyclobenzaprine hcl	263	*2.6%*	294	*2.9%*	247	*2.5%*	191	*2.0%*	245	*3.0%*
ketorolac tromethamine	88	*0.9%*	141	*1.4%*	215	*2.2%*	150	*1.6%*	196	*2.4%*
amoxicillin/clavulanate	168	*1.7%*	235	*2.3%*	146	*1.5%*	201	*2.1%*	185	*2.3%*
amoxicillin trihydrate	262	*2.6%*	311	*3.1%*	280	*2.8%*	312	*3.3%*	183	*2.2%*
cefazolin sodium	146	*1.4%*	142	*1.4%*	233	*2.3%*	171	*1.8%*	150	*1.8%*
azithromycin	85	*0.8%*	79	*0.8%*	151	*1.5%*	123	*1.3%*	130	*1.6%*
naproxen	199	*2.0%*	100	*1.0%*	163	*1.6%*	183	*2.0%*	123	*1.5%*
levofloxacin	36	*0.4%*	68	*0.7%*	30	*0.3%*	27	*0.3%*	104	*1.3%*
clindamycin hydrochloride	17	*0.2%*	54	*0.5%*	21	*0.2%*	30	*0.3%*	91	*1.1%*
penicillin v potassium	109	*1.1%*	139	*1.4%*	117	*1.2%*	122	*1.3%*	89	*1.1%*
All Others	3,734	*36.7%*	3,649	*36.2%*	3,282	*32.9%*	3,029	*32.4%*	2,412	*29.5%*
02118 ANTI-MIGRAINE,COMB	803	*2.6%*	669	*2.1%*	646	*2.0%*	547	*1.8%*	537	*1.7%*
Used Alone	457	*56.9%*	469	*70.1%*	476	*73.7%*	374	*68.4%*	313	*58.3%*
topiramate	9	*1.2%*	--	--	12	*1.8%*	5	*0.9%*	57	*10.7%*
amitriptyline hcl	50	*6.3%*	10	*1.5%*	18	*2.7%*	20	*3.7%*	42	*7.9%*
sumatriptan succinate	42	*5.3%*	7	*1.0%*	11	*1.6%*	8	*1.5%*	35	*6.5%*
divalproex sodium	14	*1.7%*	11	*1.6%*	6	*1.0%*	17	*3.0%*	21	*3.9%*
hydrocodone bitartrate/apap	10	*1.3%*	11	*1.7%*	8	*1.2%*	13	*2.5%*	14	*2.7%*
promethazine hydrochloride	22	*2.8%*	23	*3.4%*	10	*1.5%*	10	*1.9%*	14	*2.6%*
metoclopramide hydrochloride	33	*4.1%*	5	*0.7%*	--	--	5	*0.9%*	13	*2.3%*
nortriptyline hydrochloride	30	*3.8%*	25	*3.7%*	40	*6.2%*	15	*2.7%*	12	*2.3%*
duloxetine	--	--	--	--	--	--	--	--	12	*2.2%*
ibuprofen	12	*1.5%*	--	--	--	--	6	*1.0%*	8	*1.6%*
eletriptan hydrobromide	--	--	--	--	5	*0.7%*	6	*1.1%*	8	*1.5%*
acetaminophen	--	--	--	--	--	--	9	*1.7%*	8	*1.5%*
tizanidine hcl	--	--	--	--	9	*1.4%*	--	--	7	*1.4%*
amitriptyline/cl-diazepoxide	--	--	--	--	--	--	5	*0.8%*	7	*1.3%*
naproxen	2	*0.2%*	--	--	--	--	--	--	7	*1.2%*
propranolol hydrochloride	17	*2.1%*	10	*1.4%*	9	*1.4%*	19	*3.5%*	7	*1.2%*
ketorolac tromethamine	27	*3.4%*	26	*3.8%*	15	*2.3%*	11	*2.1%*	6	*1.2%*
diltiazem hydrochloride	--	--	--	--	--	--	--	--	6	*1.2%*
gabapentin	2	*0.3%*	10	*1.6%*	2	*0.4%*	11	*2.0%*	6	*1.0%*
dexamethasone acetate	14	*1.7%*	--	--	--	--	5	*0.9%*	5	*1.0%*
famotidine	11	*1.3%*	--	--	--	--	5	*0.9%*	5	*1.0%*
lorazepam	--	--	--	--	--	--	4	*0.7%*	5	*1.0%*
All Others	237	*29.5%*	123	*18.4%*	98	*15.2%*	83	*15.2%*	20	*3.6%*
All Others	222	*0.7%*	279	*0.9%*	179	*0.6%*	308	*1.0%*	273	*0.9%*

SOURCE: Verispan, PDDA, Years 2001 - 2005, Extracted Nov 2006; Source file: PDDA 2006-23 APAP class Concm Mol qry

Table 10: Total occurrences of *concurrent* drug use for the USC classes of APAP containing drug products, Years 2001 - 2005

	2001		2002		2003		2004		2005	
	Occur	*Share*	Occur	*Share*	Occur	*Share*	Occur	*Share*	Occur	*Share*
	(000)	*%*	(000)	*%*	(000)	*%*	(000)	*%*	(000)	*%*
TOTAL MARKET	30,315	*100.0%*	31,121	*100.0%*	32,094	*100.0%*	30,359	*100.0%*	31,249	*100.0%*
02120 ACETAMINOPHEN	19,127	*63.1%*	20,095	*64.6%*	21,290	*66.3%*	20,143	*66.3%*	22,254	*71.2%*
Used Alone	8,649	*45.2%*	9,356	*46.6%*	8,841	*41.5%*	8,680	*43.1%*	9,864	*44.3%*
02132 SYN NON-NARC NON-INJ	1,388	*7.3%*	1,495	*7.4%*	2,131	*10.0%*	1,646	*8.2%*	1,831	*8.2%*
15151 AMINOPENICILLINS	1,766	*9.2%*	1,648	*8.2%*	1,643	*7.7%*	1,574	*7.8%*	1,735	*7.8%*
15130 CEPHALOSPORN & RELTD	780	*4.1%*	882	*4.4%*	1,026	*4.8%*	999	*5.0%*	1,061	*4.8%*
09110 ANTIARTHRTCS SYS PLN	439	*2.3%*	416	*2.1%*	492	*2.3%*	691	*3.4%*	829	*3.7%*
15142 EXT SPECTRUM MACROLIDE	535	*2.8%*	786	*3.9%*	940	*4.4%*	820	*4.1%*	787	*3.5%*
27422 DIPHTHERIA TOX,COMB	190	*1.0%*	362	*1.8%*	568	*2.7%*	650	*3.2%*	741	*3.3%*
34120 COLD W/O ANALGESICS	871	*4.6%*	831	*4.1%*	939	*4.4%*	785	*3.9%*	738	*3.3%*
34320 CGH/CLD W/O EXPECT	481	*2.5%*	574	*2.9%*	728	*3.4%*	564	*2.8%*	641	*2.9%*
02232 CODEINE & COMB NON-INJ	318	*1.7%*	357	*1.8%*	597	*2.8%*	453	*2.2%*	518	*2.3%*
27221 PNEUMO CONJUGATE	142	*0.7%*	221	*1.1%*	458	*2.1%*	448	*2.2%*	505	*2.3%*
27330 POLIO CONTAINING	157	*0.8%*	213	*1.1%*	360	*1.7%*	354	*1.8%*	414	*1.9%*
15600 INCREASED B-LACTAM ACT	439	*2.3%*	534	*2.7%*	502	*2.4%*	410	*2.0%*	414	*1.9%*
15180 QUINOLONES	379	*2.0%*	351	*1.7%*	453	*2.1%*	427	*2.1%*	393	*1.8%*
34420 COUGH W/O CODEINE	393	*2.1%*	457	*2.3%*	434	*2.0%*	356	*1.8%*	348	*1.6%*
27130 HIB VACCINE	125	*0.7%*	168	*0.8%*	439	*2.1%*	314	*1.6%*	343	*1.5%*
15152 NATURAL PENICILLINS	285	*1.5%*	225	*1.1%*	309	*1.5%*	289	*1.4%*	340	*1.5%*
34310 CGH/CLD W/EXPECT	265	*1.4%*	175	*0.9%*	249	*1.2%*	225	*1.1%*	298	*1.3%*
14120 ANTIHISTAMINE ORAL LIQ	95	*0.5%*	69	*0.3%*	93	*0.4%*	125	*0.6%*	266	*1.2%*
59111 MUSC RLX W/O ANALG	221	*1.2%*	195	*1.0%*	204	*1.0%*	209	*1.0%*	262	*1.2%*
78800 MISC ETHICALS OTHER	194	*1.0%*	209	*1.0%*	213	*1.0%*	314	*1.6%*	260	*1.2%*
28420 INHALED STER NASAL	60	*0.3%*	122	*0.6%*	105	*0.5%*	143	*0.7%*	247	*1.1%*
14110 ANTIHISTAMINE CAP-TAB	198	*1.0%*	189	*0.9%*	263	*1.2%*	291	*1.4%*	238	*1.1%*
21220 ANTISEPTICS MTH & THR	134	*0.7%*	140	*0.7%*	138	*0.6%*	109	*0.5%*	225	*1.0%*
All Others	6,039	*31.6%*	6,247	*31.1%*	7,619	*35.8%*	6,868	*34.1%*	7,606	*34.2%*
02232 CODEINE & COMB NON-INJ	10,164	*33.5%*	10,078	*32.4%*	9,979	*31.1%*	9,361	*30.8%*	8,185	*26.2%*
Used Alone	5,161	*50.8%*	5,118	*50.8%*	5,252	*52.6%*	4,826	*51.6%*	4,319	*52.8%*
15130 CEPHALOSPORN & RELTD	823	*8.1%*	916	*9.1%*	1,036	*10.4%*	924	*9.9%*	714	*8.7%*
09110 ANTIARTHRTCS SYS PLN	663	*6.5%*	548	*5.4%*	570	*5.7%*	609	*6.5%*	642	*7.8%*
59111 MUSC RLX W/O ANALG	529	*5.2%*	552	*5.5%*	470	*4.7%*	464	*5.0%*	341	*4.2%*
02132 SYN NON-NARC NON-INJ	243	*2.4%*	199	*2.0%*	223	*2.2%*	192	*2.0%*	232	*2.8%*
15151 AMINOPENICILLINS	281	*2.8%*	344	*3.4%*	282	*2.8%*	302	*3.2%*	220	*2.7%*
15600 INCREASED B-LACTAM ACT	170	*1.7%*	233	*2.3%*	174	*1.7%*	188	*2.0%*	203	*2.5%*
15180 QUINOLONES	122	*1.2%*	152	*1.5%*	109	*1.1%*	120	*1.3%*	139	*1.7%*
15142 EXT SPECTRUM MACROLIDE	128	*1.3%*	115	*1.1%*	184	*1.8%*	157	*1.7%*	134	*1.6%*
02131 SYN NON-NARC INJ	66	*0.6%*	101	*1.0%*	148	*1.5%*	88	*0.9%*	131	*1.6%*
37210 ANTI-INF NON-SYS TOP	126	*1.2%*	241	*2.4%*	231	*2.3%*	106	*1.1%*	125	*1.5%*
15152 NATURAL PENICILLINS	138	*1.4%*	182	*1.8%*	134	*1.3%*	144	*1.5%*	107	*1.3%*
52210 CORTICOIDS PLAIN ORAL	75	*0.7%*	102	*1.0%*	75	*0.7%*	52	*0.6%*	99	*1.2%*
15149 ALL OTHER MACROLIDES	19	*0.2%*	51	*0.5%*	24	*0.2%*	48	*0.5%*	82	*1.0%*
All Others	3,458	*34.0%*	2,743	*27.2%*	2,567	*25.7%*	2,480	*26.5%*	1,763	*21.5%*

SOURCE: Verispan, PDDA, Years 2001 - 2005, Extracted Nov 2006; Source file: PDDA 2006-23 APAP class Concr Class qry

Table 10 continued on next page.

Table 10, continued: Total occurrences of *concurrent* drug use for the USC classes of APAP containing drug products, Years 2001 - 2005

	2001		2002		2003		2004		2005	
	Occur	*Share*	Occur	*Share*	Occur	*Share*	Occur	*Share*	Occur	*Share*
	(000)	*%*	(000)	*%*	(000)	*%*	(000)	*%*	(000)	*%*
02118 ANTI-MIGRAINE,COMB	803	*2.6%*	669	*2.1%*	646	*2.0%*	547	*1.8%*	537	*1.7%*
Used Alone	344	*42.9%*	399	*59.7%*	406	*62.9%*	321	*58.6%*	230	*42.8%*
20200 SEIZURE DISORDERS	34	*4.2%*	38	*5.7%*	21	*3.2%*	40	*7.4%*	72	*13.3%*
64310 ANTIDEP TRI/TETRA	88	*11.0%*	42	*6.3%*	48	*7.4%*	45	*8.2%*	54	*10.1%*
02112 SRTONIN 5HT-1 REC AGON	90	*11.2%*	31	*4.6%*	34	*5.3%*	26	*4.8%*	28	*5.1%*
15151 AMINOPENICILLINS	3	*0.4%*	5	*0.8%*	--	--	--	--	20	*3.7%*
64610 BENZODIAZEPINES	24	*3.0%*	16	*2.4%*	--	--	4	*0.7%*	19	*3.6%*
09110 ANTIARTHRTCS SYS PLN	28	*3.5%*	14	*2.1%*	--	--	12	*2.2%*	16	*3.0%*
31410 BETA-BLOCKERS	36	*4.5%*	20	*2.9%*	14	*2.2%*	25	*4.6%*	15	*2.8%*
02232 CODEINE & COMB NON-INJ	30	*3.8%*	17	*2.6%*	11	*1.8%*	30	*5.5%*	14	*2.7%*
17210 ANTNAUS ANTIDOPA PHENO	28	*3.5%*	25	*3.7%*	15	*2.3%*	10	*1.9%*	14	*2.6%*
23300 GI STIMULANTS	29	*3.6%*	5	*0.7%*	--	--	5	*0.9%*	13	*2.3%*
15142 EXT SPECTRUM MACROLIDE	8	*1.1%*	--	--	--	--	--	--	11	*2.0%*
28111 BETA AGON AEROSOL	--	--	10	*1.5%*	5	*0.7%*	--	--	10	*1.9%*
28410 INHALED STER BRONCH	0	*0.1%*	4	*0.6%*	--	--	--	--	10	*1.9%*
02132 SYN NON-NARC NON-INJ	21	*2.7%*	5	*0.8%*	7	*1.1%*	--	--	9	*1.6%*
02120 ACETAMINOPHEN	2	*0.2%*	4	*0.6%*	8	*1.2%*	13	*2.3%*	8	*1.5%*
52210 CORTICOIDS PLAIN ORAL	--	--	7	*1.1%*	--	--	5	*1.0%*	8	*1.4%*
34410 COUGH W/CODEINE	--	--	--	--	--	--	--	--	8	*1.4%*
34110 COLD W/ANALGESICS	--	--	--	--	--	--	--	--	7	*1.4%*
59111 MUSC RLX W/O ANALG	16	*1.9%*	6	*0.9%*	36	*5.6%*	5	*0.9%*	7	*1.4%*
02140 SALICYLATES & RELTD	4	*0.5%*	--	--	4	*0.6%*	--	--	7	*1.3%*
64380 ANTIDEPRESS IN COMBO	--	--	--	--	--	--	5	*0.8%*	7	*1.3%*
61220 ARTIF TEARS LUBRIC	--	--	--	--	--	--	--	--	7	*1.2%*
02131 SYN NON-NARC INJ	38	*4.7%*	30	*4.4%*	10	*1.5%*	11	*2.1%*	6	*1.2%*
31300 CALCIUM BLOCKERS	23	*2.9%*	10	*1.5%*	15	*2.3%*	8	*1.5%*	6	*1.2%*
64350 ANTI-DEPRESSANTS SNRIS	--	--	--	--	--	--	--	--	6	*1.1%*
52220 CORTICOIDS PLAIN INJ	14	*1.7%*	--	--	--	--	5	*0.9%*	5	*1.0%*
23410 H2 ANTAGONISTS	7	*0.9%*	--	--	--	--	12	*2.1%*	5	*1.0%*
64340 ANTI-DEPRESSANTS SSRIS	23	*2.9%*	11	*1.6%*	16	*2.6%*	--	--	5	*1.0%*
All Others	209	*26.1%*	96	*14.4%*	81	*12.5%*	63	*11.5%*	8	*1.5%*
All Others	222	*0.7%*	279	*0.9%*	179	*0.6%*	308	*1.0%*	273	*0.9%*

SOURCE: Verispan, PDDA, Years 2001 - 2005, Extracted Nov 2006; Source file: PDDA 2006-23 APAP class Concr Class.qry

Laura Governale, Pharm D., MBA.
Team Leader
Division of Surveillance, Research, and Communication Support (DSRCS)

Solomon Iyasu, M D, MPH
Director
Division of Surveillance, Research, and Communication Support (DSRCS)