Submitted by the
CONSUMER HEALTHCARE PRODUCTS ASSOCIATION

BRIEFING BOOK

Joint Meeting of the Drug Safety and Risk Management Advisory Committee, Nonprescription Drugs Advisory Committee, and the Anesthetic and Life Support Drugs Advisory Committee

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CONSUMER HEALTHCARE PRODUCTS ASSOCIATION (CHPA)

B R I E F I N G B O O K

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1. Executive Summary

1.1 Introduction

In the April 16, 2009, *Federal Register,* FDA announced a joint meeting of the Drug Safety and Risk Management Advisory Committee, Nonprescription Drugs Advisory Committee, and the Anesthetic and Life Support Drugs Advisory Committee to discuss the public health problem of liver injury related to the use of acetaminophen in both over-the-counter (OTC) and prescription (Rx) products. In its announcement, FDA stated that it recognized the importance of acetaminophen to treat pain and fever, and was not seeking to remove it from the market. FDA wants input from the committees on potential implementation of additional risk minimization strategies to mitigate the risk of liver injury related to acetaminophen medication errors. The Consumer Healthcare Products Association (CHPA) is the national trade association representing the leading manufacturers and distributors of OTC medicines and dietary supplements in the United States (U.S.). CHPA's members manufacture OTC acetaminophen single-ingredient and combination products for children and adults. Our priority is to ensure that parents and families have timely and cost-effective access to the best possible OTC medicines available today and that consumers and caregivers have the resources and information available to use these medications safely and appropriately. CHPA has an interest and expertise in the subject matter of the Advisory Committee meeting and is providing background information for the committee to review prior to the meeting.

The materials provided in this book address the following areas:

- OTC use of acetaminophen
- Safety and efficacy of acetaminophen combinations
- Professional treatment guidelines and recommendations
- Labeling and advertising of OTC acetaminophen products
- Pediatric acetaminophen products
- Combination products
- Pack size restrictions
- Education
- CHPA recommended actions

1.2 Background

Acetaminophen is one of the most commonly used ingredients in the U.S. to treat pain and fever. It has been available over-the-counter (OTC) to consumers for decades. It is found in single-ingredient OTC products for infants (concentrated drops), children (liquid suspensions) and adults (liquids, tablets and capsules). It is also found in combination products, where it functions as a pain reliever/fever reducer to treat menstrual pain, back pain, migraine headache, muscle aches and pain, sore throat, headache and fever associated with colds and flu, and pain with occasional sleeplessness. These products provide consumers with effective pain relief and are safe and effective when used according to labeled directions.

In the vast majority of situations, acetaminophen is used safely, but in a very small percentage of users, cases of liver injury occur. More than half of these cases are caused by Rx products. In approximately 40% of total reported cases, OTC products are involved, and of these cases, about one-half are intentional (e.g. suicide) and one-half are unintentional (e.g. medication errors or unintentional over-administration). Of all the cases, a very small percent involve OTC combination products.

CHPA strongly believes that a successful strategy to improve this public health problem will therefore need to include Rx and OTC stakeholders. It is CHPA's position that FDA's focus should be on enhanced and evidence-based education and labeling to encourage appropriate use of acetaminophen and to increase awareness of health risks associated with misuse and overdose. At the Advisory Committee meeting, CHPA will present additional information on an evidence-based education program based on new and existing research. This information will include the following:

- new consumer research to establish appropriate target audiences and root causes of consumer misuse;
- proposed interventions, validated by pre-testing; and,
- population-based, longitudinal quantitative survey data to evaluate and measure consumer attitudes and behaviors.

1.3 Efficacy

Acetaminophen is well-established as an effective OTC analgesic and fever reducer, as consumers can self-diagnose and treat intermittent minor aches and pains. Acetaminophen is approved for use in OTC medicines for adults in tablet or liquid dose strengths ranging from 325 mg to 500 mg. The recommended single dose of acetaminophen for adults is 325 to 1000 mg. Controlled clinical trials and meta-analyses show a dose-response in efficacy across this range. CHPA supports continued availability of these tablet or liquid strengths and doses, as they provide consumers with a range of choices to achieve satisfactory pain relief with effective doses of drug.

1.4 Safety

As demonstrated by multiple clinical trials and databases, the vast majority of acetaminophen is used safely. As a result, CHPA supports continued availability of tablet and liquid dose strengths ranging from 325 – 500 mg, and of single doses ranging from 325 – 1000 mg. While overdose of acetaminophen can lead to hepatotoxicity, ranging from significantly elevated liver enzyme levels to liver failure, CHPA agrees with the FDA, which stated that the potential to cause liver toxicity when used improperly is not a reason to discourage proper use of acetaminophen. Studies show doses of acetaminophen of up to 1000 mg are safe and not associated with any unacceptable risks.

Looking ahead, FDA acknowledges that research is needed to better understand toxic threshold, at-risk populations, and to track the effectiveness of interventions on acetaminophen safety. CHPA is ready to work with FDA and other stakeholders to define the research agenda needed to mitigate risk of acetaminophen overdose and liver injury.

Packaging is another important aspect of safety. Today's packaging standards and CHPA member practices protect children from inadvertent access to acetaminophen. OTC acetaminophen-containing products sold by CHPA members are sold in child-resistant packaging. Acetaminophen is covered under the Poison Prevention Act, which is administered by the Consumer Product Safety Commission. This law requires that acetaminophen-containing products be sold in child-resistant packaging. Exceptions are permitted for a limited number of products that are clearly labeled as not

intended for households with small children. In addition, all OTC acetaminophen-containing liquid products sold by CHPA member companies are sold with a product-specific, calibrated dosing device. CHPA believes that current packaging standards are appropriate and meet the criteria of protecting children from inadvertent access to these products.

1.5 Labeling and Advertising of OTC Products

Labeling of OTC acetaminophen products is regulated by FDA, primarily under the OTC Monograph system, and in a few cases, under New Drug Applications. Labels for OTC medicines at the point of sale are legally required to contain all the information the FDA has determined consumers need to select and use the medication appropriately. Single ingredient products are clearly labeled on the principal display panel and in the Drug Facts section. In 2001, recognizing that labeling of acetaminophen products could be improved, CHPA member companies developed improved labeling to strengthen warning statements and to highlight active ingredients. CHPA members voluntarily re-labeled their products in 2002-2003 and these changes remain in place today.

In addition to the label changes described above, manufacturers are also currently implementing label changes required by FDA in its Final Rule for organ-specific warnings for OTC internal analgesic products, published April 29, 2009. This rule addresses many of the points recommended by the FDA Working Group. CHPA is evaluating ways to increase consumer recognition of the presence of acetaminophen in OTC and prescription products. These include working with stakeholders across the spectrum of product availability – manufacturers, pharmacists, healthcare providers and consumers themselves.

FDA's briefing materials mention advertisements for OTC medicines not being subject to the same requirements as prescription products. In fact, OTC advertising is subject to *different* regulation. We are providing some background information on the regulatory (via the Federal Trade Commission) and self-regulatory controls over OTC advertising in Section 6 of this document.

1.6 Pediatric Use

Pediatric acetaminophen products are used frequently to treat fever in children and CHPA member companies have long recognized the importance of ensuring safe use of these products in children. CHPA agrees with the Working Group recommendation that liquid products be sold with appropriate dosing devices. In fact, for years, CHPA members have proactively provided proper dosing devices for liquid products to encourage proper dosing. For very young children, concentrated drops are dispensed with a dosing device provided with the product. For older children, liquid suspensions are dosed with dosing cups provided with the product. In addition, CHPA member companies are participating in the CDC-led initiative to reduce unintended dosing errors of pediatric products. One aspect of this initiative is to work to standardize the volumetric measures and abbreviations used for volumetric measures product labels and on dosing devices.

CHPA supports the inclusion of dosing information for children younger than 2 years on single ingredient acetaminophen-containing product labels and to physicians. Pediatricians continue to recommend acetaminophen for young children. Having this information on product labels, along with the proper dosing device, will enable parents and caregivers to dose correctly.

However, CHPA recommends caution and additional research before any decision to limit pediatric (children age 12 and younger) liquid acetaminophen formulations to one mid-strength concentration. During the transition to such a formulation there would be an extended period of time in which existing dose cups would be available in consumers' homes. The use of this dosing cup with the new, mid-strength concentration could lead to an increase in overdose events. There would need to be significant efforts to re-educate healthcare professionals who have become accustomed to recommending dosing for the currently available formulations. As such, standardizing pediatric formulations to a single concentration has potential for unintended consequences, such as overdosing and mis-dosing. Education of parents, caregivers and professionals about the proper dosing and the proper formulation should be attempted before any consideration is given to changing concentrations.

1.7 OTC Combination Products

CHPA strongly supports the continued availability of OTC combination products containing acetaminophen. Most commonly, acetaminophen is found in OTC combination products in tablet strengths of 325 – 500 mg, and doses of 650 – 1000 mg, where it functions as a pain reliever/fever reducer to treat a variety of symptoms, including fever/muscle aches associated with cold and flu, menstrual pain, back pain, migraine headache and pain with occasional sleeplessness. OTC combination products effectively treat conditions in which multiple symptoms, including pain, are present, such as the common cold, or in cases where the combination of multiple analgesics is beneficial, such as the treatment of certain types of pain.

Combination products containing acetaminophen offer simplified dosing of multiple ingredients, making the dosing more accurate and reducing the risk of medication errors. It is well-established in the medical literature that medication errors increase with each additional medicine a patient is asked to take. Lack of combination products has significant potential for serious unintended consequences.

Importantly, OTC combination products are less frequently involved in acetaminophen overdoses, to an extent that is markedly disproportionate to their use. As cited in the FDA's briefing materials, serious liver injuries are rarely due to OTC combination products (less than 10% of all cases), with many more cases attributable to Rx combination products.

CHPA strongly opposes the elimination of OTC acetaminophen containing combination products and disagrees with the assertion that combination products are only available for convenience. In contrast, these products provide for accurate dosing of multiple ingredients to effectively treat conditions where multiple symptoms are present. Maintaining OTC combination products is strongly supported by their safety profile and proven effectiveness, in addition to the accessibility, convenience, cost-savings and compliant dosing they afford consumers.

1.8 Pack Size Restrictions

The FDA Working Group considered and decided not to recommend packaging restrictions for OTC acetaminophen products. CHPA agrees with this approach, which was based on their review of the UK experience, where blister packaging, reduced count size, and point of sale restrictions were implemented. There are conflicting data about the impact of these actions on liver injury. In addition, consumers would be adversely affected by reducing pack size since they would pay more per dose for smaller pack sizes, with those taking acetaminophen frequently or chronically (and appropriately) being most affected. Larger sizes offer the best consumer value per dose for multi-person households sharing the same analgesic or consumers requiring more frequent use of an OTC analgesic.

1.9 Education

CHPA strongly supports enhanced education efforts to improve label comprehension, encourage appropriate use of acetaminophen, and to increase awareness of potential health risks associated with acetaminophen misuse and overdose. CHPA shares the FDA's education goal and has committed to work with the FDA and other stakeholders to advise and educate consumers about the importance of using acetaminophen correctly and the dangers and risks of overuse.
CHPA has already begun designing the elements of an evidence-based public health education initiative that is both targeted and comprehensive regarding the safe use of acetaminophen. The objective of the campaign is to raise consumer awareness of recent label changes, identify acetaminophen risks, and modify consumer comprehension of risk information to enhance appropriate use of acetaminophen. This educational campaign will be grounded in research, supported by science, and will be tested and validated by specific metrics. Importantly, the program will be carried out in partnership with key stakeholders, including pharmacists, healthcare providers, retailers and the FDA to ensure the program's messages are communicated widely by respected and authoritative voices and touch consumers at multiple levels for reinforcement. Specifically, the program will follow established principles for effective behavior-change programs.

1.10 CHPA Recommended Actions

Based on the data, findings, and analyses presented in this book, CHPA and its member companies are taking the following steps to encourage the appropriate use of acetaminophen-containing OTC medicines:

- We are committed to using research-based tools to better understand consumer behavior and perception and to evaluate current and future intervention.
- We are committed to leading a national education effort, partnering with FDA, CDC and other stakeholders, to raise consumer awareness of the safe use of acetaminophen in both OTC and prescription products and the risk of overdose.
- We are committed to improving the recognition of acetaminophen on OTC product labels.
- We are committed to implementing FDA's Final Rule issued on April 29, 2009, for internal analgesics.
- We will continue participation in the CDC-led initiative to reduce accidental, unsupervised ingestions of medicines and medication errors.

CHPA and its member companies have a long history of educating consumers on the safe use of OTC medicines and have taken the lead on many important initiatives over the years. From child resistant packaging to tamper-evident packaging and the development of the OTC Drug Facts label in conjunction with FDA, CHPA has been proactive and unwavering in its commitment to providing the highest quality medicines to the millions of American families who rely on them each and every day, as well as the information and tools to use these medicines appropriately. CHPA sees the recommendations outlined in this document related to acetaminophen as a continuation of this long standing commitment.

The materials provided in this document reflect the collective work and views of the following CHPA member companies which currently market OTC products containing acetaminophen:

Bayer Healthcare LLC

GlaxoSmithKline

McNeil Consumer Healthcare

Novartis Consumer Health, Inc.

Perrigo Company

The Procter & Gamble Company

Schering-Plough Healthcare Products, Inc.

Wyeth Consumer Healthcare

2. Over-the-Counter Acetaminophen – Medication Use and Place in Therapy

2.1. Medication Use

KEY POINTS

- Acetaminophen is the most commonly used drug ingredient in the United States.
- In any given week, 23% of adults report using an acetaminophen-containing product including over-the-counter (OTC) single-ingredient and combination products as well as prescription (Rx) narcotic/acetaminophen combination medicines.
- About 61% of the usage of all acetaminophen-containing products is with OTC medicines and 39% with Rx narcotic/acetaminophen combination products.
- Among the OTC medicines, approximately 56% of products are OTC combination formulations and 44% are OTC single-ingredient acetaminophen products.

A survey of close to 2,600 adult participants conducted by the Slone group showed that acetaminophen is the most frequently used drug ingredient in the United States. Twenty-three per cent (23%) of the participants reported having used an acetaminophen-containing product in the previous week. The use of acetaminophen was almost evenly spread between men and women and among the age groups 18 – 44 years, 45 – 64 years, and ≥ 65 years.[1]

An FDA report from 2006 examined the use of OTC and Rx products containing acetaminophen as measured by units sold. The key findings of this analysis were that approximately 29 billion extended units (tablets/capsules/milliliters of solution) of acetaminophen-containing products were sold to retail and non-retail pharmacies during the year 2005. Of these, approximately 17.5 billion extended units (61%) were OTC medicines and 11 billion (39%) were Rx narcotic/ acetaminophen combination products. Fifty-six per cent (56%) were combination and 44% were single-ingredient OTC products*. For OTC acetaminophen single-ingredient products, the 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.[2]

* *A list of acetaminophen-containing OTC products on the US market is provided in the Appendix.*

2.2. Place in Therapy

KEY POINTS

- Due to acetaminophen's favorable benefit-risk ratio and its cost-effectiveness, leading U.S. and international medical associations recommend acetaminophen as a first-line treatment option in various conditions associated with pain and fever.
- These recommendations apply both to the general population and to subpopulations including children and the elderly.
- In addition, for tension-type and migraine headaches, leading associations recommend analgesic combination products containing acetaminophen.

Due to its positive benefit-risk ratio, the strong body of evidence for acetaminophen from controlled clinical trials, and its cost effectiveness, acetaminophen is the most widely recommended and used OTC pain and fever relieving medicine in the United States and worldwide. This is reflected by treatment recommendations for various conditions associated with pain, including tension-type headache and migraine headache, musculoskeletal pain, perimenstrual pain, pain and fever from upper respiratory infections, and for perioperative pain management. Some of the leading medical associations recommending acetaminophen as a first-line pain treatment choice are the National Headache Foundation, the Institute for Clinical Systems Improvement, the American College of Rheumatology, the American Pain Society, the American College of Physicians, the American Academy of Orthopaedic Surgeons, the Osteoarthritis Research Society International, the Association of Women's Health, the Obstetric and Neonatal Nurses (WWHONN), the American Academy of Family Physicians, and the American Society of Anesthesiologists.[3] [4] [5] [6] [7] [8] [9] [10] [11] [12]

In addition to the extensive scientific evidence and in-use experience with acetaminophen that supports its use as the mainstay of analgesics in the general population, acetaminophen is also recommended for use in children and older persons.

The American Academy of Pediatrics recommends acetaminophen for the treatment of fever in childhood infections in all pediatric age groups.[13]

A guideline developed by a joint subcommittee of the American Academy of Pediatrics and the American Academy of Family Physicians recognizes acetaminophen and ibuprofen as mainstays of pain management for acute otitis media, as they provide effective analgesia and are readily available.[14]

The American Geriatrics Society recommends that acetaminophen "be considered as initial and ongoing pharmacotherapy in the treatment of persistent pain, particularly musculoskeletal" because of its demonstrated effectiveness and good safety profile.[15]

Acetaminophen is used in all stages of pregnancy and is considered a drug without teratogenic effects.[16]

In its guidelines for acute pain management in the perioperative setting published in 2004, the American Society of Anesthesiologists concludes that the literature supports the administration via a single route of two analgesics that act by different mechanisms to provide superior analgesic efficacy with equivalent or reduced adverse effects. The guidelines also recognize that nonsteroidal anti-inflammatory drug (NSAID), cyclooxygenase-2 inhibitor (COXIB), or acetaminophen administration has a dose-sparing effect for systemically administered opioids.[17]

For tension-type headache and migraine headache, leading associations recommend combination analgesics containing acetaminophen. The 2004 National Headache Foundation guideline recommends aspirin and/or acetaminophen with the addition of caffeine if single-ingredient analgesics fail to produce an adequate response.[18]

In its guideline of 2000, the US Headache Consortium* recommends the fixed combination of acetaminophen plus aspirin plus caffeine, as well as aspirin, ibuprofen, naproxen, and tolfenamic acid as first-line treatment choices for mild-to-moderate migraine attacks or severe attacks.[19]

*The US Headache Consortium consists of the American Academy of Family Physicians, the American Academy of Neurology, the American Headache Society, the American College of Emergency Physicians, the American College of Physicians, the American Society of Internal Medicine, the American Osteopathic Association, and the National Headache Foundation

2.3. Combination Products

KEY POINTS

- CHPA strongly supports the continued availability of combination products containing acetaminophen.

- Combination products offer simplified dosing of multiple ingredients, making the dosing more accurate and reducing the risk of medication errors.

- The efficacy of acetaminophen as a component of combination products has been substantiated through controlled clinical trials.

- Acetaminophen combination products effectively treat conditions, such as the common cold, in which multiple symptoms - including pain, fever or sleeplessness - are present, or in cases where the combination of multiple analgesics is beneficial, such as the treatment of migraine headache.

According to a 2005 report of the World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparations, fixed-dose combinations have potential advantages over single-ingredient medicinal products including better patient adherence, lower cost, simplified logistics of procurement and distribution, and convenience for prescribers and patients.[20]

Combination products simplify dosing and reduce the risk of medication errors, in that patients do not have to follow different dosing regimens as might be necessary when they take two or more single-ingredient products simultaneously. Combinations ease the “pill burden” since patients don’t have to take several single-ingredient products simultaneously to obtain the desired symptom relief. And finally, it is more affordable for patients to purchase a combination product than to purchase, for example, an analgesic plus a cold product, separately.

Data published in peer-reviewed journals demonstrate a 25 % reduction of the risk of patient non-compliance with recommended dosing when a combination product is used relative to concurrent

single-ingredient product use. A systematic review from 2007 summarizes the findings of 9 studies in which fixed-dose combination medications were compared against the single-drug medications given simultaneously (example: 1 tablet of enalapril hydrochlorothiazide versus enalapril and hydrochlorothiazide given as 2 separate tablets). Two of these studies were in patients with tuberculosis, 4 in the hypertensive population, 1 in patients with human immunodeficiency virus (HIV) disease, and 2 in the diabetic population. Almost 12,000 patients on fixed-dose combinations were compared against more than 8,000 patients on concurrent single-ingredient product therapy. Across the 9 studies, combination products reduced the risk of non-compliance to the recommended dosing schedule by 24 % - 26%. The difference in compliance in favor of combination products was statistical significant in 7 out of the 9 studies.[21]

Similar to aspirin and several NSAIDs, acetaminophen is used as a component of two types of combination products:

1) **Combination analgesics:** combinations of ingredients with an additive or synergistic effect for the symptomatic treatment of pain (such as the combination of acetaminophen, aspirin, and caffeine for headache)
2) **Multi-symptom combinations:** combinations of multiple ingredients for conditions with multiple symptoms (such as the combinations of acetaminophen with oral nasal decongestants for headache, sinus pain, fever, and stuffy nose in common cold)

Acetaminophen as a Component of Combination Analgesics

The rationale for acetaminophen combinations with other analgesics, such as aspirin, tramadol, and opioids, lies in the enhancement of pain relief by combining two analgesics with different modes of action. Other benefits of combining analgesics include increasing the duration of analgesia and widening the spectrum of efficacy.[22] [23]

Acetaminophen as a Component of Combination Cough and Cold Products

The rationale for using acetaminophen as a component of cough and cold products is based on the fact that patients experience a range of symptoms concurrently in the common cold. In these products, acetaminophen provides the analgesic and antipyretic activity that adds to the symptom

relief achieved by other ingredients that may be targeted on more specific symptoms such as nasal decongestion or cough. Research in naturally acquired and artificially induced colds confirms that the symptoms tend to occur in a predictable pattern over the 7 to 10 days of a typical uncomplicated infection (Table 1).[24] [25] [26] [27]

Table 1. The frequency of cold symptoms in adults [adapted from Witek et al. 1992]

	Frequency of cold symptoms (%)						
SYMPTOM	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
Nasal congestion	87	93	94	89	85	82	72
Runny nose	82	85	81	71	62	53	49
Sore throat	78	66	52	45	34	28	23
Cough	51	64	61	62	54	49	44
Sneeze	67	64	57	49	40	31	25
Headache	62	63	54	44	37	28	24

Another study published in 2005 found that, in adults, symptoms which were reported at least once during the first 7 days of a common cold were: nasal symptoms (99% of participants), sore or scratchy throat (90%), cough (94%), sinus pain or pressure (80%), chest congestion (73%), headache (88%), body ache (84%), feverishness (69%), sweats (55%), and chills (57%).[28]

A recent study examined cold symptoms in children aged from 2 through 12 years. The most common reported symptoms at their maximum prevalence over 10 days were nasal congestion (88%), runny nose (72%), cough (69%), and sneezing (55%). Fever and headache were each reported in 15% of children at onset of the cold.[29]

These data, coupled with the findings of Turner and Tyrrell in induced colds, emphasize the medical desirability for treatment of pain and fever together with other symptoms of the common cold. For the vast majority of uncomplicated cold episodes in adults and children, treatment with OTC combination medicines, including combinations of acetaminophen with antitussives, nasal decongestants, antihistamines, or expectorants, helps to achieve this objective.[30] [31]

3. Efficacy and Safety of Acetaminophen

3.1. Efficacy

KEY POINTS

- The efficacy of acetaminophen at the currently recommended strengths, and at the currently recommended single and daily doses has been well-established. This provides consumers with a range of choices to achieve satisfactory pain relief in fever and various types of pain, with effective doses of drug.

- The efficacy of acetaminophen as a component of combination products was also substantiated through controlled clinical trials, including studies with factorial design. These multi-armed trials show the superior benefit of combination products over both the individual ingredients taken alone and placebo.

3.1.1. General Efficacy

The efficacy of acetaminophen has been well-established as a pain reliever and fever-reducer in children and adults. Acetaminophen is approved for use in OTC medicines for adults in tablet or liquid dose strengths ranging from 325 mg to 500 mg. The recommended single dose of acetaminophen for adults is 325 mg to 1000 mg. A robust body of data, including an extensive number of controlled clinical trials, demonstrate acetaminophen's efficacy at the currently available formulation strengths, as well at the currently recommended single and daily doses. Controlled clinical trials and meta-analyses show a dose-response in efficacy across this range. In addition to a large number of individual studies in various conditions associated with pain and fever, the results of systematic reviews and meta-analysis demonstrate the efficacy of acetaminophen at the currently recommended dose levels.[32] [33] [34] [35] [36] [37] [38]

3.1.2. Efficacy of Combination Products

Tension-Type and Migraine Headache

A 1994 publication by Migliardi et al. summarizes the results of 6 randomized, double-blind, crossover studies enrolling a total of 1,900 patients in which the combinations of acetaminophen, aspirin, and caffeine were evaluated for relief of tension-type headache. In all 6 studies the acetaminophen combination products, i.e., both acetaminophen/aspirin/caffeine and acetaminophen/caffeine combinations studied, were significantly superior to placebo, indicating the benefit of these combination products for common headache conditions.[39]

Lipton et al. (1998) summarizes the efficacy of the acetaminophen/aspirin/caffeine combination from 3 clinical trials in migraine headache patients. All 3 trials were of similar design - double-blind, placebo-controlled, parallel group studies - and randomized a total of more than 1,300 subjects who had moderate to severe migraine. The results from all 3 clinical studies show that the analgesic combination of acetaminophen, aspirin, and caffeine is effective in treating migraine headache. Statistically significant improvement was also found for the migraine-associated symptoms of nausea, phonophobia, photophobia, and associated disability.[40]

Additionally, a post-hoc analysis of the above-mentioned 3 clinical studies in migraine patients evaluated a subset of subjects who had severe, disabling migraine. A statistically superior benefit was observed for the triple-ingredient combination on pain response and pain intensity, further supporting the effectiveness of the acetaminophen/aspirin/caffeine combination in the subset of migraine sufferers with the most severe symptoms.[41]

Further post-hoc analyses were obtained from the same studies regarding menstruation-associated migraine. Menstrual migraine is an important concern, as migraine is more prevalent in women and associated with the occurrence of menses. The OTC combination of acetaminophen, aspirin and caffeine was evaluated to determine if were as effective for treating menstrual migraine as it is for migraine not associated with menses. The acetaminophen/aspirin/caffeine combination was found to be significantly effective versus placebo in relieving the pain, disability, and associated symptoms of both menstruation-associated migraine and migraine not associated with menses.[42]

A study by Goldstein et al. published in 2006 compared an acetaminophen/aspirin/caffeine combination to ibuprofen and placebo for the relief of acute migraine. There were more than 1,700 randomized patients in this study, which included patients with migraine of all severities. The results of this study demonstrate that the acetaminophen/aspirin/caffeine combination and ibuprofen were more effective than placebo in treating the full spectrum of migraine. Acetaminophen/aspirin/caffeine was found to be superior to ibuprofen as evidenced by the statistically significant and clinically greater effects for the primary endpoint: the sum of pain relief (PAR) scores at 2 hours. Additionally, acetaminophen/aspirin/ caffeine was found to be superior to ibuprofen for pain intensity reduction, earlier onset of PAR, and headache response.[43]

Further, in another recent clinical study (the ASSET Trial), the acetaminophen/ aspirin/caffeine combination has been shown to be significantly more effective than sumatriptan and placebo as assessed by the sum of pain intensity differences, as well as for secondary endpoints including pain relief, pain intensity reduction, sustained response, and relief of associated symptoms. The results from the ASSET study suggest that migraine sufferers can treat migraine episodes, with the analgesic combination of acetaminophen, aspirin, and caffeine, at the first sign of a migraine attack. [44]

Recent studies with factorial design demonstrated that the triple-combination combination of acetaminophen, aspirin and caffeine is more effective than single substances and dual combinations for the treatment of tension-type and migraine headache.[45] [46]

Common Cold

One of the main goals of controlled clinical trials with combination products for the treatment of conditions with multiple symptoms is to demonstrate that the combination maintains the benefit of each component. This was, for example, shown in a randomized, double-blind, parallel design study in about 430 adult subjects by Mizoguchi et al. (2007) which examined the benefit of treating multiple symptoms of common cold with a combination of acetaminophen with dextromethorphan doxylamine, and ephedrine. A single night-time dose of the combination or placebo was given to subjects with at least moderate nasal congestion and a runny nose, at least mild cough, and at least mild pain with one or more of the following: sore throat, sore chest, headache, or body aches and pain. Subjects' subjective scoring of symptoms 3 hours after dosing and within 1 hour after rising

the next morning found clinically and statistically significant relief with the combination versus placebo for the primary endpoint (composite of nasal congestion/runny nose/cough/pain relief scores 3 hours post-dosing). Each individual symptom score was also significantly improved at 3 hours. In the group taking the combination product the percentages of subjects rating their symptoms as improved related to baseline were: nasal congestion 55.4% (versus 44.7% at placebo), runny nose 58.9% (versus 51% placebo), cough 56.7% (versus 43.3% at placebo), and pain 55.4% (versus 38.9% at placebo).[47]

In a double-blind, parallel design study, Eccles et al. (2006) found that a combination of acetaminophen with pseudoephedrine for symptomatic treatment of upper respiratory tract infection (URTI) provided better pain relief than either pseudoephedrine alone or placebo. A total of more than 300 adult subjects with nasal congestion from an URTI and a global pain score of at least moderate intensity were randomized to receive the combination product, acetaminophen alone, pseudoephedrine alone, or placebo. Nasal airflow resistance and pain relief/intensity scores were measured over 4 hours after the subjects had taken the first dose. The subjects then took doses up to three times daily for 3 days and recorded nasal congestion and pain intensity scores. The primary outcomes in this study were nasal airflow conductance and pain relief after the initial dose. A single dose of the combination was statistically superior to pseudoephedrine alone and placebo for pain relief and was statistically superior to acetaminophen alone and placebo for nasal airway conductance. Multiple doses of the combination were also statistically superior to pseudoephedrine alone and placebo for pain reduction and to acetaminophen and placebo for decongestion.[48]

Loose & Winkel also showed that a combination of acetaminophen with pseudoephedrine was effective in symptomatic treatment of nasal congestion and muscle ache associated with common cold. Their study, published in 2004, was a double-blind, randomized, placebo-controlled, parallel-group comparison to investigate the effect of a single dose of the combination medicine over 6 hours on the symptoms. There were more than 150 adult subjects in each study arm. The acetaminophen/pseudoephedrine combination was statistically significantly more effective than placebo for relieving both nasal congestion and for reducing the intensity of muscle ache.[49]

3.2. Safety

KEY POINTS

- At the currently recommended strengths and doses, acetaminophen has a track record of safety with millions of people over decades of use.

- In very rare cases, people who take more than the recommended dose can develop liver injury.

- In order to understand the incidence rates and the root causes of acetaminophen overdoses and to adopt the appropriate preventive measures, it is important to differentiate among the different types of overdose: intentional versus unintentional overdoses, cases with Rx narcotic/acetaminophen combination products versus OTC products (OTC single-ingredient and combination products), and finally taking more than one acetaminophen-containing medicine.

- Data from the American Liver Failure Study Group (ALFSG) show that intentional misuse (suicide attempts) accounts for 44% of acute liver failure cases. Unintentional overdose accounts for 48% of cases. The reason for the overdose was unclear in the remaining 8% of cases.

- The ALFSG data show that 56% of the acute liver failure cases result from overdoses of Rx narcotic/acetaminophen combination products compared to 44% associated with the use of OTC acetaminophen products.

- OTC combination products are less frequently involved in acetaminophen overdoses, to an extent that is markedly disproportional to their use. In an FDA analysis of acetaminophen-related death cases, only 6% of cases were found to be associated with OTC combination products. Rx narcotic/ acetaminophen combination and OTC single-ingredient products accounted for 59% and 33% of cases, respectively.

- An FDA analysis has also shown that about 10% of acetaminophen-related deaths were associated with the use of more than one Rx narcotic/ acetaminophen combination product and/or OTC acetaminophen product.

3.2.1. General Safety

Acetaminophen is the most frequently used drug ingredient in the United States and has a track record of safe and effective use over decades and in millions of people. Acetaminophen is, therefore, regarded as a first-line therapy in management of pain by numerous leading professional organizations (see Section 2.2.).

In a *Federal Register* notice of April 24, 2009, FDA recognizes acetaminophen's favorable safety profile and states: *"… acetaminophen is considered safe when used according to the directions on its OTC or Rx labeling. However, taking more than the recommended amount can cause liver damage, ranging from abnormalities in liver function blood tests, to acute liver failure, and even death. Many cases of overdose are caused by patients inadvertently taking more than the recommended dose (i.e., 4 grams a day) of a particular product, or by taking more than one product containing acetaminophen (e.g., an OTC product and an Rx drug containing acetaminophen)."*[50]

Acetaminophen has very few drug interactions and is recommended for use in children and older persons. When an analgesic or antipyretic medicine is indicated in pregnancy, acetaminophen is deemed as safe for use in pregnant women.[51] [52] [53]

3.2.2. Overdose

The occurrence of acetaminophen overdose in rare cases is a public health concern. Adults and children can develop liver injury if they ingest acetaminophen overdoses.

<u>Intentional Versus Unintentional Overdoses</u>

A significant number of acetaminophen overdose exposures in the United States occur when individuals take massive doses of the substance in a suicide attempt. This was shown in analysis of

acetaminophen exposures recorded from 2003 to 2005 in the Toxic Exposure Surveillance System (TESS) * conducted by FDA's Office of Surveillance and Epidemiology. The study showed that about 60%-70% of the fatal exposures associated with OTC single-ingredient acetaminophen products as well as with Rx narcotic/acetaminophen combinations were with suicidal intent. Approximately 10%-25% of exposures were unintentional or accidental exposures. Relative to OTC single-ingredient products and Rx narcotic/acetaminophen combinations, a significantly lower number of both intentional and unintentional exposures was associated with OTC combination products (unintentional exposures associated with OTC combinations were limited to single cases only) (*Table 2*.).[54]

* TESS is the poisoning surveillance database maintained by the American Association of Poison Control Centers

Table 2. Fatalities associated with acetaminophen, TESS

Year	OTC Single-Ingredient Products			OTC Combination Products			Prescription Narcotic/ Acetaminophen Combinations		
	Total N =	Suicide (%)	Uninten-tional (%)	Total N =	Suicide (%)	Uninten-tional (%)	Total N =	Suicide (%)	Uninten-tional (%)
2003	114	71 (62)	26 (23)	22	18 (82)	0	78	50 (64)	8 (10)
2004	110	69 (63)	20 (18)	22	20 (91)	1 (4)	86	64 (74)	11 (13)
2005	96	57 (59)	25 (26)	20	14 (70)	1 (5)	72	46 (63)	8 (11)

A study published in 2006 by investigators of FDA's Office of Drug Safety used data from different national databases (2 emergency room databases, a hospital discharge database, a national mortality file, and the TESS poison surveillance database) to obtain estimates of acetaminophen-associated overdoses. In the various databases between 47% and 75% of overdose cases were intentional, self-harm episodes.[55]

A high proportion of intentional overdoses was also seen in a prospective study of 275 patients with acetaminophen-related acute liver failure enrolled at the 22 American Liver Failure Study Group centers. Forty-four percent (44%) of these cases resulted from intentional overdoses. Forty-eight percent (48%) of patients experienced an unintentional acetaminophen overdose. In 8%, the reason for the overdose was unclear.[56]

The situation is different in children. In one recent report, acetaminophen-related acute liver failure was attributed to unintentional overdoses in all of the 16 enrolled children (≤ 14 years). An FDA analysis of pediatric cases of acetaminophen-related liver injury showed that dosing errors was the predominant root cause for hepatotoxicity, followed by accidental ingestions, forced ingestion/child abuse, and the use of the wrong formulation (concentrated drops 100 mg/ milliliter instead of suspension 32 mg/ milliliter).[57] [58]

Overdoses With Prescription Versus Over-the-Counter Products

Both OTC acetaminophen products and Rx narcotic/acetaminophen combination products are associated with overdoses leading to acute liver failure. The ALFSG data as reported by Larson et al. provide information about those cases. They show that 56% of the cases were associated with OTC medicines compared to 44% associated with Rx narcotic/acetaminophen combinations. Among the group with unintentional acetaminophen exposures, 63% had used Rx narcotic/ acetaminophen combinations compared to 18% of cases with intentional overdoses. More than 80% of acute liver failure cases in the group who had intentionally overdosed with acetaminophen were associated with use of OTC medicines compared to approximately 40% in the unintentional group.[59]

Overdoses Associated With OTC Combination Products

Analyses of data from various sources indicate that OTC combination products are less frequently involved in acetaminophen overdose exposures, to an extent that is markedly disproportional to their use. (Nota bene: combination products account for 56% of unit sales and single-ingredient products for 44%. See Section 2.1.). The FDA analysis of acetaminophen exposure cases recorded from Toxic Exposure Surveillance System (TESS) showed that in 2005 there were 67,531 exposures reported to poison centers for OTC single-ingredient acetaminophen products compared to 7,083 exposures (which is just over 10% of the number of exposures in the OTC single-ingredient group) for OTC acetaminophen combination products.[60] [61]

An FDA study examined reports of acetaminophen-related deaths from 2005 in the agency's Adverse Event Reporting System (AERS). Only 5 out of 81 cases (6%) were associated with OTC combination products compared to 48/81 (59%) and 27/81 (33%) cases associated with Rx narcotic/acetaminophen combinations and OTC single-ingredient products, respectively.[62]

In an analysis of the data for the combined years 2004-2005 conducted by a collaboration of various governmental agencies, the ratios of emergency department visits associated with acetaminophen-containing products was lowest for OTC combination products. The ratio of emergency department visits between Rx narcotic/ acetaminophen combinations, OTC single-ingredient products, and OTC combination products was approximately 6.5 : 2.5 : 1.[63]

Overdoses Associated With the Use of More Than One Product

Acetaminophen overdose exposures associated with the simultaneous use of more than one acetaminophen-containing Rx narcotic/acetaminophen combination product and/or OTC acetaminophen medicine have been seen in various studies. While there is no doubt that these findings should be addressed through appropriate measures, the data also show that the "unintentional doubling" factor must not be overestimated. In the above-mentioned FDA analysis of acetaminophen-related death cases from 2005, about 10% of cases were associated with the use of more than one product compared to 90% associated with the use of only one product.[64]

In the ALFSG study examining 275 patients with acetaminophen-induced acute liver failure, more than one acetaminophen-containing product was used by 38% of subjects in the intentional exposure group but by only 5% in the unintentional group.[65]

4. Labeling

4.1 Package Labels of OTC Medicines

Unlike prescription drugs, package labels of OTC medicines at the point of sale are legally required to contain all the information that the FDA has determined consumers need to appropriately select and use the product, as defined by the appropriate Monograph or NDA approved labeling. As of 2001, OTC label information is required to be presented in the standardized Drug Facts format, which clearly calls out active ingredients, dosing information and warnings, and other important information.

Most acetaminophen product labels are governed by the OTC Monograph system. Changes to product labels regulated under the OTC Monograph system can take years due to the required steps of the administrative rule making process. In 2001, manufacturers made voluntary label changes, without rulemaking, with FDA's full knowledge of the initiative. These voluntary label changes, outlined below, remain in place today. Recently, many of these changes were incorporated into FDA's Final Rule for organ-specific warnings for OTC internal analgesics products, published April 29, 2009. An example of how these new warnings will be incorporated into the Drug Facts label is shown at the end of this section.

4.2 CHPA Voluntary Acetaminophen Labeling Initiative

In 2001, CHPA member companies that sold OTC single ingredient and combination acetaminophen products conducted an extensive root cause analysis of their post-marketing surveillance data to better understand serious adverse events associated with acetaminophen. As a result of that analysis, it was agreed that labeling would be enhanced to increase awareness of the presence of acetaminophen in the product and warn consumers about the serious consequences of taking more than the recommended dose. Executives of leading OTC companies met with FDA in December 2001 to outline their proposed label changes.

The changes listed below were then implemented during 2002-2003, with manufacturers of single ingredient and combination acetaminophen products voluntarily re-labeling their products (except for sample sizes):

- display active ingredients of combination products on the Principal Display Panel (single ingredient products already displayed active ingredients on the PDP, as required by law);
- include "consumer-friendly" language describing the purpose of the ingredient, such as "minor aches and pains" instead of "analgesic";
- add a new warning: *Do not use with other medicines containing acetaminophen*;
- add a label flag to highlight the presence of new label information; and
- highlight the Active Ingredients section of the Drug Facts label in yellow, or other contrasting colors;
- add a new warning: Overdose warning: *Do not exceed the recommended dose*; and
- add new directions: *Do not take more than directed*.

4.3 FDA Final Rule for Organ-Specific Warnings for OTC Analgesics

On April 29, 2009, FDA issued a Final Rule[1] requiring manufacturers of OTC pain relievers and fever reducers to revise product labels to include organ-specific warnings about potential safety risks, such as stomach bleeding and liver damage, associated with the use of these products. Ingredients covered under the final rule include acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs). All products containing these ingredients, including pain relievers and cold and flu medicines for multi-symptom relief, must be relabeled within one year. A general OTC product label for acetaminophen showing the changes required under this Final Rule is shown at the end of this section.

[1] Federal Register/Vol. 74, No. 81/April 29, 2009 [pages 19385-19409} (Final Rule) Organ-Specific Warnings; Internal Analgesic, Antipyretic, and Anti-rheumatic Drug Products for Over-the-Counter Human Use; final Monograph [21 CFR Part 201/docket No. FDA-1977-N-0013]

Requirements under the Final Rule for acetaminophen-containing products include (paraphrased):

- Prominently displaying the active ingredients on the drug labels (primary package and outer package, if applicable).
- Label warning: Severe liver damage may occur if taking more than the maximum daily amount, with other drugs containing acetaminophen, or with high alcohol consumption
- Label warning: Ask a doctor before using if liver disease is present
- Label warning: Ask a doctor or pharmacist before using if you are taking warfarin
- Label warning: Do not use with any other drug containing acetaminophen

Manufacturers are now making these changes to their product labels. During 2009, these labeling changes will begin to appear on store shelves. Consumers will be alerted to the new information on labels with the addition of a prominent "flag" on the front of the outer carton or product label (if there is no outer carton) that states "see new warnings information". This flag will remain on the cartons or labels for 12 months and thereby maximize the opportunity of alerting consumers to these changes. These labels will be a key component of the education program to ensure consumers understand the importance of knowing when a product contains acetaminophen and the potential risks of taking too much of this medicine.

CURRENT OTC ACETAMINOPHEN LABEL WARNINGS	NEW OTC ACETAMINOPHEN LABEL WARNINGS Final Monograph 21 CFR 201, April 29, 2009
Drug Facts	Drug Facts
Warnings Alcohol warning: If you consume 3 or more alcoholic drinks every day, ask your doctor if you should take acetaminophen or other pain relievers/fever reducers. Acetaminophen may cause liver damage.	**Warnings** Liver warning: This product contains acetaminophen. Severe liver damage may occur if you take ▪ more than (insert maximum number of daily dosage units) in 24 hours, which is the maximum daily amount ▪ with other drugs containing acetaminophen ▪ 3 or more alcoholic drinks every day while using this product
Do not use with any other drug containing acetaminophen.	Do not use with any other drug containing acetaminophen (prescription or nonprescription). If you are not sure whether a drug contains acetaminophen, ask a doctor or pharmacist.
	Ask a doctor before use if you have liver disease.
	Ask a doctor or pharmacist before use if you are taking the blood thinning drug warfarin.
Stop use and ask a doctor if ▪ pain gets worse or lasts for more than 10 days ▪ fever gets worse or lasts for more than 3 days ▪ new symptoms occur ▪ redness or swelling is present	Stop use and ask a doctor if ▪ pain gets worse or lasts for more than 10 days ▪ fever gets worse or lasts for more than 3 days ▪ new symptoms occur ▪ redness or swelling is present
If pregnant or breastfeeding, ask a health professional before use. Keep out of reach of children. In the case of overdose, get medical help or contact a Poison Control Center right away. Quick medical attention is critical for adults as well as for children even if you do not notice any signs or symptoms.	If pregnant or breastfeeding, ask a health professional before use. Keep out of reach of children. In the case of overdose, get medical help or contact a Poison Control Center right away. Quick medical attention is critical for adults as well as for children even if you do not notice any signs or symptoms.

Note: Yellow highlighting is for emphasis only.

5. Education

CHPA believes that in addition to the label, education is one of the most important and effective interventions in changing consumer attitudes and behaviors. The association has a long and successful history of educating consumers about the safe and appropriate use of its products and remains committed to ensuring that consumers have all the information they need to make important health decisions for themselves and their families.

The CHPA Acetaminophen Task Group, working through CHPA's Educational Foundation – OTCsafety.org – FDA, and key stakeholders, is well positioned and committed to implementing an educational campaign as it pertains to the appropriate use of acetaminophen. CHPA, through its educational foundation and OTCsafety.org, already has developed important information for consumers on the safe use of acetaminophen and other OTC pain relievers.

CHPA and its member companies already have committed to working with FDA and other key stakeholders to undertake a comprehensive educational campaign, intended to raise awareness among consumers and healthcare professionals about the potential risk of acetaminophen overdose and the potential for liver injury while also encouraging safe use practices. Specific, targeted messages would be focused around:

- Taking no more than the recommended dose of acetaminophen,
- Not mixing acetaminophen-containing products, prescription and OTC, and
- Reading and following the label warnings and directions and speaking to a doctor or other healthcare professional as recommended.

CHPA strongly supports efforts to encourage appropriate use of acetaminophen and to increase awareness of potential health risks associated with acetaminophen overdose. CHPA supports FDA's goal of enhancing public education efforts and already has begun considering design elements of a public health education initiative that is both targeted and comprehensive. This educational campaign will be grounded in research, supported by science, and tested and validated by specific metrics. CHPA will base the program both on existing and new research to establish target audiences and deepened insights on root causes of consumer misunderstanding and

misuse. The research will empirically test interventions and will rigorously evaluate the results, using agreed upon survey data.

A large factor in the success of the proposed campaign will be to ensure it is addressing the root causes of overdose. Because some of the potential opportunities for overdose involve both OTC and prescription medicines, it is important that educational messages and partners include all key stakeholders, including FDA, physicians, pharmacists, and other healthcare professionals and organizations. CHPA is partnering with the American Pharmacists Association (APhA) to create a consortium of key parties such as these that will actively participate in this educational campaign.

Overall, education is an important and effective intervention when utilized correctly. CHPA has a proven track record of developing successful campaigns, working with partners from multi-disciplinary sectors, and employing the newest and most innovative techniques to target consumers.

Acetaminophen Education Campaign

Goal: Reduce acetaminophen overdose and liver injury.

Objective #1: Increase awareness and change perceptions among users of acetaminophen-containing products about the risks associated with overdose.

Rationale: Low awareness and health literacy rates may be a contributing factor to the overdose of acetaminophen.

Activity:

- Targeted Education and Outreach Program
- Develop and testing messages geared to particular at risk audiences.
- Create working partnerships with FDA, CDC, healthcare professionals, and consumer and patient groups.
- Distribute messaging through multiple, focused channels (including traditional and online communications).

Criteria to Verify Success:

- Establish criteria to monitor awareness of overdose.
- Test messages for education and outreach with consumers through rigorous qualitative and quantitative methodology.
- Field a bi-annual quantitative survey to assess progress and success and identify any needed adjustments.

Critical Milestones:

- Schedule regular meetings with FDA to present findings, messages, and align on any necessary plan adjustments.

Objective #2: Modify behaviors of targeted populations to help increase the number of consumers taking the recommended dose of acetaminophen.

Rationale: Consumers who are taking more than the recommended dose of acetaminophen are not following the directions on the label or believe that taking more than the recommended dose will provide them with faster, better relief.

Activities:

- Targeted Education and Outreach Program
- Develop and test messages geared to particular audiences.
- Identify and reach target audiences in relevant situations (OTC single ingredient, OTC combination, or prescription products).
- Utilize “teachable moments” and “real-life experiences” to influence consumer behaviors.
- Identify proper vehicles to educate at point of consumption.

Criteria to Verify Success:

- Test key messages to ensure they are impactful and enduring among relevant audience.
- Identify most at-risk populations and messages that resonate best.
- Field a bi-annual quantitative survey to assess progress and success and identify any needed adjustments.

Critical Milestones:

- Schedule regular meetings with FDA to present findings and messages, and align on any necessary plan adjustments.

Partners

CHPA understands that the most effective program will include the key stakeholders responsible for communicating information to consumers and patients about the appropriate use of acetaminophen and possible risks associated with misuse and overdose. CHPA has reached out to a number of these groups and organizations and has received many favorable responses and interest regarding participation in these efforts. Additionally, CHPA and APhA are putting together a key consortium of organizations to play a prominent role in disseminating information to consumers.

CHPA and APhA will use this consortium to refine strategies, leverage resources, enhance reach, echo messages, and evaluate success. It is important that external organizations appreciate their role and responsibility in educating consumers about the potential risks of acetaminophen misuse. Below is a list of committed organizations to date. We anticipate additional organizations and agencies joining the effort.

U.S. Food and Drug Administration
American Pharmacists Association
American Academy of Family Physicians
Alliance for Aging Research
National Association of Chain Drug Stores
National Council on Patient Information and Education

6. Regulation of Advertising of OTC Products

6.1 Introduction

FDA's options paper states that "advertisements of OTC drugs are not required to provide warning information." The agency is correct that advertising of OTC medicines is subject to different requirements than apply to prescription medicines. This distinction is based in law and sound policy.

Labels for OTC medicines at the point of sale, unlike those for prescription drugs, are legally required to contain all the information that FDA has determined consumers need to select and use them appropriately. Because a consumer is given complete information through labeling, requiring a wider range of information in OTC medicine advertising is unnecessary. Further, with prescription medicines, a patient can only receive a medicine through a learned intermediary, whose presence is necessary because of the drug's toxicity or other potentiality for harmful effect, method of use, or collateral measures necessary to its use. By definition, the safety and use profiles of OTC medicines are such that they do not require this intervention, including acetaminophen in OTC formulations.

Manufacturers can and do encourage appropriate use of their products through advertising. As the February 2008 working group report states, the regulation of OTC advertising is the role of the Federal Trade Commission. The FTC and FDA have long had a memorandum of understanding to clarify their complementary roles around labeling as contrasted with advertising.[2]

[2] Memorandum of Understanding Between Federal Trade Commission and the Food and Drug Administration, 36 Fed. Reg. 18539 (September 16, 1971).

6.2 Advertising standards and controls

There are a number of regulatory and self-regulatory controls over OTC advertising, which require that all advertising be truthful and not misleading.

FTC advertising standards. The FTC's authority over advertising, including advertising for OTC medicines, is summarized under three basic regulatory standards: the prior substantiation doctrine, deception policy, and unfairness policy.

Prior substantiation. Prior substantiation drives at whether an claim is true or not. FTC requires that all claims, whether express or implied, be supported by adequate substantiation before the ad is disseminated. In looking at claims for OTC medicines, FTC generally looks to FDA determinations or works with the agency.[3]

Deception policy. FTC's deception policy looks to real life situations and how consumers would interpret an advertisement or, more technically, at practices that are likely to cause injury to consumers by affirmatively misleading their informed choice (this includes either misrepresentations or omissions).[4] "Injury" in the FTC sense is a broader concept than an approach FDA would typically take in considering a warning label, in that it includes economic or monetary harm as well.

Unfairness policy. Distinct from deception, unfairness looks at circumstances under which a practice causes a consumer injury that is: (1) substantial; (2) not outweighed by countervailing consumer or competitive benefits that the practice produces; and (3) one which consumers could not reasonably have avoided.[5]

[3] Eve E. Bachrach, *Over-the-Counter Drug Advertising: FTC and FDA Concerns*, 7 Food, Drug and Cosmetic Section Newsletter (New York State Bar Association), September 1990, at 7.
[4] See *International Harvester Co.,* 104 F.T.C. 949 (1984).
[5] See *International Harvester*, supra. Congress later acted to translate the International Harvester three-pronged definition into law. See 15 USC sec. 45(n) ("The Commission shall have no authority under this section or section 57a of this title to declare unlawful an act or practice on the grounds that such act or practice is unfair unless the act or practice causes or is likely to cause substantial injury to consumers which is not reasonably avoidable by consumers themselves and not outweighed by countervailing benefits to consumers or to competition. . . .")

Enforcement activity. The FTC has been active is using its authority against violative advertisements, initiating more than 200 enforcement actions challenging false and misleading health and safety claims for products whose claims ranged from weight-loss to curing cancer. In 2008, the FTC initiated or resolved 17 law enforcement actions involving a range of products allegedly making deceptive health claims.[6]

Self-regulatory advertising controls. Beyond the FTC, companies marketing OTC medicines have to be familiar with four other mechanisms used to assure OTC medicine advertisements are truthful and not misleading. First, companies have their own internal approval steps for advertisements, which typically include medical/scientific, legal, regulatory, and general management review.

Second, the major television networks have their own clearance, or program practices departments, which must be satisfied with an advertisement before the network will accept it. Documentation to support claims can become important in this review.

Another mechanism is the National Advertising Division (NAD) of the Council of Better Business Bureaus. NAD investigates complaints based on staff identification, challenges by competitors, or complaints from other parties (including consumers or local Better Business Bureaus) based on the truth and accuracy of the advertisement. After screening, complaints go through a judicial-style process, after which NAD prepares a final case decision that is published. Decisions typically report on both NAD's views and the advertiser's plans to respond to the decision, such as supporting substantiation, modifying the advertisement, or discontinuing the advertisement. NAD refers cases to the FTC or other authorities where appropriate, including where an advertiser does not respond to a decision. In most cases, however, NAD decisions result in the fast and efficient removal of violative claims from the marketplace. In 2008, the NAD adjudicated 9 challenges to advertising claims for OTC drugs such as antiperspirants, antihistamines, acne treatments, antifungals, and anticaries toothpaste.[7] An even broader range of non-drug, health-related advertising claims were challenged.

Fourth and finally, competitive forces play an important role in how companies approach their advertising. Firms may choose to litigate under the Lanham Act, which creates a private right of

[6] See http://www.ftc.gov/os/actions.shtm, listing FTC actions by month.
[7] See National Advertising Division latest cases listing at http://www.nadreview.org/search/search.aspx?doctype=1&casetype=1.

action when an advertiser misrepresents its products or a competitor's product where the conduct causes a significant competitive injury.[8] The threat of litigation in itself is a deterrent for major product manufacturers from deceptive or misleading advertising.

Ultimately, the objective of OTC medicine advertising is to raise consumer awareness that there are products that can provide relief of symptoms associated with a self-treatable illness or condition, and is therefore fundamentally different from prescription drug advertising that communicates the availability of drugs that require consultation with a physician. OTC advertising is then complemented at the point of purchase with complete Drug Facts labeling that allows consumers to select the medicine that is right from them.

7. CHPA Recommended Actions

CHPA and its member companies forming the Acetaminophen Task Group are committed to continuing to improve the safe use of OTC products containing acetaminophen by U.S. consumers. Member companies, with FDA and other stakeholders, are taking the following actions to ensure acetaminophen is used safely:

- We have already begun research and are committed to conducting an evidence-based national education campaign that addresses the root causes of consumer misunderstanding and misuse of acetaminophen.

- The goal of the program will be to raise awareness among consumers and healthcare professionals about the potential risk of acetaminophen overdose and the potential for liver injury, while also encouraging safe use practices. CHPA will base the initiative on both existing and new research which will empirically test interventions. We will also rigorously evaluate the results, using agreed upon survey data. Because acetaminophen-related overdose involves both OTC and prescription medicines, an important part of the program will be CHPA's partnership with key stakeholders, including FDA, pharmacists, physicians,

[8] See Lanham Act sec. 43(a), 15 USC sec. 1125(a).

and other healthcare professionals and organizations, that will actively participate in this educational campaign.

- We are committed to implementing FDA's Final Rule issued on April 29, 2009, for internal analgesics, which will include improving the recognition of acetaminophen on OTC product labels

- Manufacturers are currently changing labels on acetaminophen-containing products to reflect the requirements in the Final Rule. These changes will begin appearing on store shelves this year. They include adding language in the warning section of labels that explicitly warn about severe liver damage if taking more than the maximum daily dose, with other drugs containing acetaminophen, or with high alcohol consumption. Manufacturers will also prominently display the active ingredients on the drug labels. For the next 12 months, these label changes will be further highlighted with the addition of a prominent "flag" on the front of the outer carton or product label that states "see new warnings information."

- We will continue participation in the CDC-led initiative to reduce accidental, unsupervised ingestions of medicines and medication errors.

- Since November 2008, CDC has led a collaborative effort among university scientists, medical researchers, FDA and CHPA staff and member company representatives with the goal of reducing accidental, unsupervised ingestions of pediatric medicines. There are four working groups focused on root cause analysis, packaging solutions, education and standardizing volumetric measures. Over the next year, the collective output of this initiative, from education to new technologies, has the potential to significantly improve consumer understanding of proper dosing of OTC medicines.

CHPA and its member companies have a long history of educating consumers on the safe use of OTC medicines and have taken the lead on many important initiatives over the years. From child resistant packaging to tamper-evident packaging and the development of the OTC Drug Facts label in conjunction with FDA, CHPA sees the recommendations outlined in this document related to acetaminophen as a continuation of this long standing commitment.

8. Appendix

OTC Products on the US Market that Contain Acetaminophen

OTC Products that Contain Acetaminophen			
Brand	Product	Brand	Product
Alka-Seltzer Plus	Day-Non Drowsy Cold Formula Liquid Gels	**Panadol**	500
	Night Cold Formula Liquid Gels		PM
	Cold & Cough Formula Liquid Gels		Cold & Flu
	Day & Night Cold Formulas Liquid Gels		Cold & Flu Non-Drowsy
Anacin	Aspirin Free Pain Reliever		Liberacion Rapida
	Advanced Headache Formula		Menstrual
Arthriten	Joint Pain Relief Formula		Back Pain
Backaid	Maximum Strength Back Relief		Childrens Liquid
Benadryl	Allergy Sinus Headache		Childrens-infant Drops
	Severe Allergy & Sinus Headache		Childrens Chewable
	Allergy and Cold	**Percogesic**	Aspirin-Free Pain Reliever
Comtrex	Maximum Strength Day & Night Cold and Sinus	**Premsyn PMS**	Maximum Strength Premenstrual Relief
	Maximum Strength Non Drowsy Cold & Cough Relief	**Robitussin**	Robitussin Night Time Cough Cold & Flu
	Deep Chest Cold		Robitussin Night Time Cough & Cold D
	Non Drowsy Cold & Cough	**Singlet**	Tablets
	Severe Cold and Sinus	**Sinutab**	All Products
Contac	Cold & Flu Maximum Strength	**Sudafed**	Cold & Sinus Liquid Caps
	Cold & Flu Maximum Strength Non Drowsy		Severe Cold Caplets and Tablets
	Day & Night Cold and Flu		Sinus Headache Caplets and Tablets
Coricidin HBP	Antihistamine Cough & Cold Suppressant	**TheraFlu**	All Regular and Maximum Strength Caplets and Hot Liquid
	Cold and Flu Tablets for People	**Triaminic**	Flu
	Maximum Strength Flu		Cough & Fever Liquid
	Nighttime Multi-Symptom Cold Relief		Cough & Sore Throat Liquid
Dristan	Cold Multi-Symptom Tablets		Cough & Sore Throat Softchews
Diurex	PMS Formula	**Tylenol**	Sinus Severe Congestion Caplets
Excedrin	All Products		Severe Allergy
FeverAll	Acetaminophen Suppositories, Juniors Ages 6-12 yrs		Arthritis Pain Extended Relief
	Acetaminophen Suppositories, Children Ages 3-6 yrs		Cold Formula
	Acetaminophen Suppositories, Infants Ages 3-36 mo.		Cold & Flu
Goody's	Extra Strength		Extra Strength Pain Reliever
	Body Pain		Flu Formula
	PM		Maximum Strength Sore Throat Adult Liquid
	Cool Orange		PM Pain Reliever/Sleep Aid
Mejoral	500		Regular Strength
Mejoralito	Chewable		Sinus
Midol	Menstrual Complete Caplets		Women's Tylenol
	Menstrual Complete Gelcaps		Junior Tylenol
	Teen Formula Caplets		Children's Tylenol
	PM Caplets		Children's Tylenol Plus
Ornex	Nasal Decongestant and Analgesic	**Vanquish**	Caplets
	Maximum Strength Nasal Decongestant and Analgesic	**Vicks**	Formula 44 Custom Care Cough & Cold PM Liquid
Pamprin	Multi-Symptom		Formula 44 Custom Care Body Aches Liquid
	Cramp		NyQuil Cold/Flu Relief Liquid, LiquiCaps and Caplets
	Maximum Strength		DayQuil Cold/Flu Relief Liquid, LiquiCaps and Caplets

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