Bayer Consumer Care Division

Review of the Safety and Efficacy of Bayer's OTC Monograph Analgesic Products

NDAC Briefing Document

Non-prescription Drug Advisory Committee (NDAC) Meeting

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Glossary of Abbreviations and Terms

ACC	American College of Cardiology
AERS	Adverse Events Reporting System
ADR	Adverse Drug Reaction
AHA	American Heart Association
ARAMIS	Arthritis, Rheumatism, and Aging Medical Information System
FDA	U.S. Food and Drug Administration
GI	Gastrointestinal
MI	Myocardial Infarction
NDA	New Drug Applications
NDAC	Non-prescription Drug Advisory Committee
NSAID	Nonsteroidal Anti-Inflammatory Drug
OTC	Over-the-Counter
PDR	Physicians Desk Reference
SLE	Systemic Lupus Erythematosus
TIA	Transient Ischemic Attach
TESS	American Association of Poison Control Centers' Toxic Exposure Surveillance System
TFM	Tentative Final Monograph
WHO	World Health Organization

1 EXECUTIVE SUMMARY

The Bayer Corporation has broad marketplace experience across the approved classes of over-the-counter (OTC) analgesics and extensive experience with their safety and effectiveness. It is Bayer's position that all of the currently approved OTC analgesics when used according to package labeling are safe and effective. Bayer's monograph analgesic products include a range of cough-cold combination formulations (Alka-Seltzer Plus), menstrual products (Midol), and a single-ingredient product Bayer Aspirin. All of these products are well established in the marketplace and have been used safely by millions of consumers over many years.

In contrast to Bayer's favorable safety experience with its acetaminophen combination products, recent reports indicate that acetaminophen overdose has become the most common cause of acute liver failure in the United States. The Nonprescription Drug Advisory Committee (NDAC) has been asked to review the market experience with acetaminophen with attention to the identification of factors that may contribute to this problem, and to recommend measures that will reduce the risk of unintentional overdose with acetaminophen. While hepatotoxicity is not a significant problem with aspirin, the NDAC has also been asked to identify factors that may contribute to the risk of GI bleeding associated with aspirin, and to make recommendations regarding appropriate measures, if any, that could better inform consumers and reduce the risk. Bayer appreciates the opportunity to address these issues and to work with FDA and NDAC to ensure that consumers continue to benefit from OTC analgesic products in the market that are safe and effective.

A review of the literature as well as the data provided by FDA indicates that the risk profile of hepatotoxicity associated with acetaminophen is very different from the risk profile of gastrointestinal bleeding associated with aspirin as described below:

Hepatotoxicity from acetaminophen overdose is dose-dependent and often associated with daily doses higher than the OTC recommended dose. The majority of cases are associated with single-ingredient products or prescription combination products. A substantial number of cases involve the concomitant use of more than one acetaminophen-containing product. Alcohol, hepatotoxic drugs, underlying liver disease, and nutritional status are clearly identified risk factors. Significantly, available data suggest that the risk from OTC acetaminophen combination products, such those marketed by Bayer, is less than for single-ingredient OTC products. This is likely due to the self-limiting conditions for which these OTC combination products are used and the presence of other active ingredients that produce dose-limiting signs and symptoms before excessive dosing can occur.

The risk profile for serious gastrointestinal events associated with aspirin is distinctly different from the market experience with acetaminophen overdose. A substantial portion

of the patients who experience serious gastrointestinal events with aspirin are adults using an aspirin product for its cardiovascular or cerebrovascular indications. These patients are taking low-dose aspirin for prolonged periods under a physician's care. The concomitant use of more than one aspirin-containing product is not a factor. Significant risk factors identified in these patients are advanced age, concomitant use of medications that might increase the risk of GI bleeding, history of ulcer, and serious medical illness. It is noteworthy that these patients follow a long-term daily regimen distinct from the typical pattern of OTC use; they are generally older, burdened with concurrent illnesses, and more susceptible to adverse events. Nevertheless there is wide acceptance that the medical benefit of appropriately managed aspirin treatment for vascular disease more than offsets the risk of gastrointestinal complications.

Because of the distinctly different risk patterns associated with the use of acetaminophen and aspirin, it is critical that the product labeling for these OTC analgesics be distinct. In dealing with the risk of accidental overdose and hepatotoxicity from acetaminophen, Bayer cautions the FDA not to impose a broad non-specific warning across all OTC analgesic monograph ingredients. It is Bayer's position that a broad, non-specific warning across all analgesics would not be adequate to warn consumers of the specific risks associated with acetaminophen. Non-specific product labeling, in effect, would dilute the message. Bayer supports strengthened warnings of the potential for hepatotoxicity related to inadvertent overdose with acetaminophen. Accordingly, Bayer has voluntarily adopted for its acetaminophen-containing products the proposed labeling drafted by the Consumer Healthcare Products Association (CHPA).

We expect that some manufacturers will argue that appropriate label modifications for acetaminophen-containing products will cause consumers to switch to other OTC analgesic products that confer a higher risk. This argument is flawed for two reasons. First, there are no data to support the view that an appropriate, balanced warning for acetaminophen will cause a significant number of patients to switch to another OTC analgesic. Secondly, it is not clear that the overall risk of aspirin used in an OTC context exceeds the overall risk of acetaminophen. Available data indicate that both the absolute number and the rate (per billion tablets sold) for all fatalities associated with acetaminophen overdose in the United States significantly exceeds the corresponding figures for aspirin overdose.

The NDAC will also review the factors that may contribute to an increased risk of GI bleeding associated with aspirin. The Committee should note that the current labeling for aspirin OTC products explicitly warns consumers of the risk of GI injury in individuals with persistent or recurrent stomach conditions. Nevertheless, Bayer is committed to do everything possible to ensure that its products are used safely to the benefit of the consumer. Accordingly, Bayer is prepared to work with the FDA to identify patient risk factors associated with the use of OTC aspirin and to pursue measures that might reasonably reduce the risk of adverse events.

This document provides Bayer's perspective on the safety and efficacy of OTC products containing the monograph analgesics acetaminophen and aspirin. Our perspective is supported by an extensive review of the literature. As an aid to the Committee we have summarized our conclusions with respect to key questions on regulatory measures that may come before the Committee. These are tabulated in Section 7 of this document and reproduced for the Committee's convenience in the pages immediately following this section.

RESPONSES TO QUESTIONS POSED TO THE COMMITTEE

The FDA will propose a number of questions regarding possible actions to enhance analgesic safety. These questions may consider regulatory action on combination products, dosing, labeling and packaging restrictions.

This table highlights some key questions that may be raised during the NDAC discussion of regulatory action to ensure safe use of acetaminophen and aspirin. With respect to acetaminophen, questions will be directed to hepatotoxicity; with respect to aspirin questions will be directed to gastrointestinal effects.

Bayer's Position on Questions Regarding Specific Regulatory Actions to Ensure Safe Product Use

Combination Products	*Acetaminophen*	*Aspirin*
Should OTC combination products be reformulated to eliminate Acetaminophen?	**Should be reviewed and discussed** OTC combination products containing acetaminophen are not significantly involved in unintended liver injury or fatalities from acetaminophen. *RX combination* products and OTC single-ingredient products are responsible for majority of unintended liver injury and for overall fatalities from acetaminophen. (FDA briefing information)	There are very few OTC aspirin combination products in the market. Use is often self-limited because of indication and effect of other active ingredients. Aspirin combination products not significantly involved in reported cases of gastrointestinal toxicity and the consequence of an acute overdose is generally less severe.

Dosing	*Acetaminophen*	*Aspirin*
Should the amount of acetaminophen per dosage unit be limited (i.e., eliminate Extra-Strength [500 mg and 650 mg] dose forms)? **Should similar action be taken with aspirin products (i.e., eliminate Extra-Strength doses)?**	**Should be reviewed and discussed** Incidence and severity of liver injury with acetaminophen is dose-related. 500-mg acetaminophen-containing products appeared to be most implicated in FDA review of US cases of liver injury. (FDA briefing information)	Most cases of GI toxicity from aspirin are patients taking aspirin at doses of less than or equal to 325 mg per day as part of a long-term RX regimen for cardiac or cerebrovascular indications under physician supervision. Higher dose strengths are required for efficacy in OTC pain or fever indications, e.g., migraine. OTC use pattern is episodic and not long-term.

Labeling	*Acetaminophen*	*Aspirin*
Should the FDA require more explicit OTC label warnings regarding the potential for cross dosing (e.g., "This product contains acetaminophen. Do not use with any other products containing acetaminophen. Your total daily dose of acetaminophen should not exceed 2000 mg per day.")	**Should be reviewed and discussed** Bayer supports inclusion of a liver-specific warning on acetaminophen-containing products as well as strengthened warnings on the hazards of taking multiple acetaminophen products simultaneously. Lowering the daily dose limit should be discussed. Hepatotoxicity is dose-related and may occur at doses less than 4 grams/day.	There are few aspirin combination products on the market, and cross dosing with aspirin-containing products is rare. Most cases of GI toxicity associated with aspirin are at doses less than or equal to 325-mg daily as part of a long-term RX regimen for cardiovascular or cerebrovascular disease. Higher dose strengths are required for efficacy in OTC pain and fever indications. Use pattern is episodic and not long-term for OTC indications.

Labeling	*Acetaminophen*	*Aspirin*
Should the FDA strengthen the label regarding liver toxicity; provide information regarding conditions and situations that may increase the risk of liver toxicity (e.g., alcohol use and abuse, underlying liver disease, certain co-medications, chronic under-nutrition, prolonged fasting)? **Should FDA do the same with GI toxicity associated with aspirin?**	**Should be reviewed and discussed** Bayer supports a liver-specific warning on all acetaminophen products. Alcohol, underlying liver disease, and some medications were potential contributing factors in FDA case series of liver injury from acetaminophen (FDA briefing information)	Aspirin OTC products are already responsibly labeled to warn consumers to ask a doctor before use "if you have stomach problems (such as heartburn, upset stomach, or stomach pain) that continue or come back, bleeding problems, ulcers." and include other appropriate warnings. Most cases of GI bleeding associated with aspirin occur in patients taking aspirin for cardiovascular indications under physician supervision. (FDA briefing information)
Packaging	*Acetaminophen*	*Aspirin*
Should the FDA limit the number of acetaminophen doses per package or require a blister pack configuration? **Should similar limitations regarding blister packing and the number of doses per package be applied to aspirin?**	**Should be reviewed and discussed** Acetaminophen overdose is the most common cause of acute liver failure in the US (Of these cases approx. 60 % accidental – 40 % suicide.) Accidental toxicity occurs when patients consume larger than recommended amounts for pain relief. Limiting package size may prevent cases (Lee, 2001).	Episodic high doses are not implicated in GI toxicity associated with aspirin. Packaging restrictions may be a hardship for elderly persons taking aspirin for cardiovascular or cerebrovascular indications or inflammatory arthritis under a physician's care.

2 INTRODUCTION

The Bayer Corporation appreciates this opportunity to address the safety of over-the-counter (OTC) analgesics and looks forward to working with the Food and Drug Administration (FDA) and Non-prescription Drugs Advisory Committee (NDAC) to ensure that consumer use of analgesics is associated with the greatest benefit and acceptable risk. This document provides Bayer's perspective on the safety of OTC analgesics and responds to questions posed by the FDA regarding the safety of OTC analgesic ingredients.

Bayer is a worldwide leader in the development and marketing of OTC analgesics. Aspirin was introduced into the market in 1899, and since has become a common household product, with over one billion tablets sold worldwide every year. Since its introduction, aspirin has provided consumers with relief of minor aches and pains and fever reduction. To this day, the benefits of aspirin are widely recognized. In fact, aspirin is continually gaining new indications for use under the direction of physicians, and is the topic of current research efforts in the areas of cardiovascular health and cancer prevention. As such, aspirin plays an important role in promoting public health.

Since the introduction of aspirin, Bayer has been a research leader in the development of analgesic ingredients and has expanded its line of analgesic products. The Bayer product line includes "new drugs," such as naproxen sodium (Aleve®), and ibuprofen (Midol®), as well as "old drugs," such as aspirin (Bayer Aspirin®), and acetaminophen (Alka-Seltzer Plus®, Midol®, Vanquish®). "New drugs" are the subject of unique New Drug Applications (NDAs), which establish each ingredient as safe and effective based on a rigorous pre-marketing review of pre-clinical and clinical data. Alternatively, "old drugs" are regulated by the Monograph process [Internal Analgesic, Antipyretic and Antirheumatic Drug Products for Over-the-Counter Human Use; Tentative Final Monograph (TFM), which establishes conditions under which OTC analgesic, antipyretic and antirheumatic drugs products are generally recognized as safe and effective (FDA, 1988)]. The TFM not only establishes safe dose levels, but also mandates what must be included in the labeling of products incorporating these ingredients to ensure their safe and effective use.

Bayer is in a unique position to comment on the safety and efficacy of OTC analgesic ingredients.

With its broad ingredient experience, Bayer is in a unique position to comment on the safety and efficacy of OTC analgesic ingredients in a balanced manner. Bayer supports efforts by the FDA to identify patient risk factors that may be associated with the use of OTC analgesics and consideration of measures that could be taken to reduce the risk of adverse events. Bayer also supports measures to encourage consumers to use all OTC products in accordance with the approved labeling. These measures could include a variety of means, including changes to class labeling, intended to better educate and

inform the consumer. Since each drug class represented among the approved OTC analgesic drugs has its characteristic pharmacology and adverse event profile, Bayer believes that changes to labeling that are identical across all OTC analgesics are scientifically inaccurate and do not serve the public interest.

While Bayer adheres to the labeling requirements set forth in the TFM, it is committed to continuous evaluation of safety signals that would require labeling enhancements to ensure the safe use and responsible marketing of its products. For example, in collaboration with the FDA, Bayer was proactive in implementing the Reye's syndrome warning on aspirin prior to the compliance date. Likewise, based on its evaluation of the acetaminophen hepatotoxicity data that suggest that acetaminophen is the most common cause for drug- induced acute liver failure in the United States (Lee, 2001), Bayer has recently made proactive changes to labeling not currently required by the FDA to enhance the safe use of its acetaminophen-containing products.

As a part of its commitment to safety, Bayer strongly supports the use of product labeling to promote safe self-medication use.

3 BAYER POSITION

All currently approved OTC analgesic ingredients are associated with an acceptable margin of safety when used as directed and offer benefit in the relief of minor to moderate pain and fever. Aspirin, when used under a physician's guidance, provides life-saving cardiovascular and anti-inflammatory benefits.

Both aspirin and acetaminophen offer analgesic and antipyretic effects. However, these ingredients have different pharmacologic properties, which result in unique therapeutic and safety profiles. It follows that the OTC analgesics differ in their indicated uses. (See Section 8.2 for approved product labeling, as well as current packaging and labels). Aspirin, for example, is indicated for use under the guidance of a physician for treatment of inflammatory conditions and for management of cardiovascular events. Acetaminophen does not share these indications.

In light of differences in indications, it is important to assess risk-benefit of these ingredients within the context of the indication. Importantly, the OTC indications of mild to moderate pain relief and fever reduction represent short term use for self-limiting conditions in which the benefit to risk relationship is

Product labeling should be enhanced to promote safe and effective self-medication.

highly favorable. The risk of adverse events increases in chronic use conditions; however, these indications are for use under physician guidance and associated with an acceptable risk-benefit.

Consumer use surveys suggest that 80% of consumers use product labeling to influence purchasing decisions (American Pharmaceutical Association, 1997). Given the unique properties of analgesic ingredients and the importance of product labels as decision-making tools for self-medicating consumers, labeling should clearly differentiate among products and ingredients. Broad labeling that generalizes across all OTC analgesic would reduce the ability of consumers to distinguish the unique benefits and risks of individual ingredients and may inaccurately suggest that products are interchangeable. Additionally, general warnings are less likely to be heeded, and are likely to obscure the importance of the intended warning.

Specific labeling among OTC analgesics is especially important in light of existing consumer confusion regarding analgesic safety and indications for use. Years of competitive advertising, for example, have persuaded many consumers and health care professionals to assume that acetaminophen is safer than aspirin, in spite of adverse event reports from a variety of sources that clearly show that this is not the case. (See Section 8.5 for a complete safety overview). Consumer confusion regarding analgesic benefits and risks is further highlighted by data suggesting that nearly 23% of people self-medicate with OTC analgesics other than aspirin for desired cardiovascular benefits (Heart Information Network, 2001). This confusion highlights the need for ingredient–specific information, as the consumer is best served by clear and concise labeling that guides appropriate product use.

3.1 Acetaminophen and Hepatic Risk

Bayer acknowledges the rationale for additional efforts to ensure safe and effective use of acetaminophen combination products.

Recent findings that suggest that the risks of hepatotoxicity with acetaminophen are greater than previously thought, may warrant additional product labeling.

Each of Bayer's acetaminophen combination products is indicated for specific uses in specific patient populations, and offers consumer convenience in the management of associated symptoms. However, Bayer is aware that because acetaminophen is included in a variety of product types, it is possible for consumers to be unknowingly exposed to acetaminophen in excess of recommended doses.

In light of the potential hepatotoxicity risks associated with acetaminophen, Bayer has strengthened the labeling on its cough-cold/allergy products to inform consumers about the potential for injury with overdose, and has voluntarily included the CHPA proposed

labeling, on products containing acetaminophen (Alka-Seltzer Plus®, Midol®, and Vanquish®). Section 8.3 highlights Bayer's proposed labeling changes that address the safety issues concerned with acetaminophen use, and highlights the suggested labeling by CHPA.

Bayer supports the inclusion of a liver-specific warning on acetaminophen-containing products, as well as strengthened warnings on the hazards of taking multiple acetaminophen-containing products simultaneously.

The recent concerns related to hepatotoxicity with acetaminophen are not relevant to aspirin. Patients receiving aspirin at prescription doses may exhibit elevations of serum hepatic enzymes, but these rarely progress to liver failure. Thus, it is Bayer's position that a liver-specific warning an aspirin products is not appropriate and likely to confuse the consumer.

Some manufacturers have purported that strengthened labeling for acetaminopehn would result would result in consumers switching to products containing other ingredients, including aspirin, which could lead to an increased risk of adverse events. These arguments are not substantiated by any data and should not be the basis for regulatory action. It is more likely that warnings specific to acetaminophen would result in increased consumer understanding, awareness and action.

Enhanced liver safety warnings on aspirin are not supported by the data and are likely to be confusing.

3.2 OTC Analgesics and Renal Effects

Concern has been raised recently about potential renal effects of the nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin. The risks of renal adverse events due to OTC analgesic use, however, are currently labeled for on NSAID- and aspirin-containing products. In addition, it should be noted that the risk of renal events with short-term, OTC dosing of NSAIDs is relatively low and renal effects generally reverse after cessation of treatment.

3.3 Aspirin and GI Injury

Aspirin has long been associated with risk of GI injury. Current aspirin labeling addresses the risk of GI injury with aspirin use, and short-term use in accordance with label instructions is not associated with high risk of GI injury. While long-term or high-dose aspirin may increase the risk of adverse GI events, it should be noted that other OTC analgesic ingredients, including acetaminophen, have also been associated with GI injury. In fact, the apparent high association of GI events with aspirin use may be due, in part, to

a recall bias in which consumers and/or physicians correlate GI injury with aspirin use in situations in which aspirin is not the primary contributor.

3.4 Aspirin for Cardioprotection and Concomitant Analgesic Use

Recent study data have highlighted concern regarding concomitant use of aspirin for cardioprotection and NSAID-containing analgesic products. In particular, there is concern that ibuprofen use in conjunction with aspirin use may decrease aspirin's cardioprotective effects. This drug-drug interaction could cause adverse cardiovascular events otherwise reduced with aspirin use. Based on this concern, consumers should be warned of the potential interaction, as more research is conducted to fully evaluate the interactions between NSAIDs and aspirin.

4 SAFETY AND EFFICACY OF BAYER PRODUCTS

Bayer Consumer Care markets a number of different analgesic products containing aspirin and/or acetaminophen indicated for relief of general pain, menstrual pain, and conditions associated with a common cold. Additionally, Bayer® Aspirin is indicated for use in cardiovascular disease and inflammatory conditions. Each Bayer product offers unique benefits and is specially formulated for use by specific patient populations. When used according to the package directions, Bayer's analgesic products are clearly safe and effective, as outlined below. A complete review of specific ingredient efficacy and safety data is presented in Sections 8.4 and 8.5, respectively.

4.1 Acetaminophen-Containing Combination Products: Alka-Seltzer Plus®, Vanquish®, Midol®

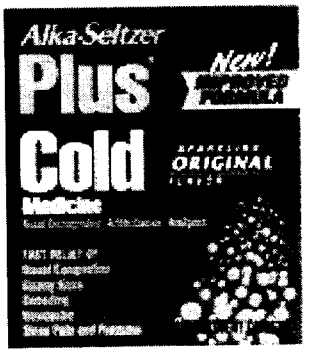
Bayer currently markets a number of acetaminophen-containing combination analgesic and antipyretic formulations, but does not offer any single ingredient acetaminophen-containing products. Combination products, which typically contain one analgesic ingredient plus one or more other active ingredient, such as a nasal decongestant, antihistamine, cough suppressant or antacid, are available OTC to treat common symptoms often occurring with pain and fever (Beaver, 1984).

Bayer's combination product line includes Alka-Seltzer®, Alka-Seltzer Plus®, Vanquish®, and Midol®. When used as directed, Alka-Seltzer®, Alka-Seltzer Plus®, Vanquish®, and Midol® provide meaningful consumer benefits, are safe and effective, and are rarely associated with adverse events. The efficacy and safety of Bayer's acetaminophen-containing products are reviewed below.

4.1.1 General Efficacy

Each of the ingredient combinations in Bayer's combination products have been proven to be effective for their indicated use, as each combination is generally recognized as effective in the Internal Analgesic Tentative Final Monograph (FDA, 1988) or corresponding Antacid, Menstrual Drug Products or Cough/Cold/Antihistamine, Antitussive, Bronchodilator, Combination, Expectorant or Nasal Decongestant Product Monographs. Acetaminophen, which is included in Bayer's combination products, is established as an effective agent for short-term use (three to ten days) for mild to moderate pain relief or fever reduction (FDA, 1988). The efficacy of each acetaminophen-containing Bayer combination product is outlined below.

4.1.1.1 Alka-Seltzer Plus®



Alka-Seltzer Plus® is a line of combination products indicated for the temporary relief of the following cold, flu and allergy symptoms: body aches and pains; coughing; fever; headache; nasal and sinus congestion; runny nose; sneezing; and sore throat. As highlighted in Table 1, there are several different Alka-Seltzer Plus® products, each containing different combinations of ingredients, intended for treatment of specific indications.

In addition to acetaminophen, the other active ingredients in Alka-Seltzer Plus® offer a full range of benefits in relief of common cold, allergy and flu symptoms. Chlorpheniramine maleate and doxylamine succinate, (antihistamines), help relieve runny nose and sneezing; dextromethorphan hydrobromide temporarily suppresses a nonproductive cough; and phenylephrine hydrochloride and pseudoephedrine hydrochloride are nasal decongestants that help restore free breathing by shrinking swollen nasal tissue and relieving sinus congestion. The therapeutic effect of each ingredient in the Alka-Seltzer Plus® combination products is outlined in Table 2.

Table 1: Active Ingredients in Alka-Seltzer Plus® Products

Combination Ingredients (Per Tablet)	Cold Effervescent	Cold Liqui-Gels	Flu Liqui-Gels	Cold and Sinus Effervescent	Cold and Sinus Liqui-Gels	Night Time Cold Liqui-Gels	Cold and Cough Liqui-Gels	Nose and Throat Effervescent
Acetaminophen	250 mg	325 mg	325 mg	250 mg	325 mg	325 mg	325 mg	250 mg
Chlorpheniramine maleate	2 mg	2 mg					2 mg	2 mg
Phenylephrine hydrochloride	5 mg			5 mg				5 mg
Pseudoephedrine hydrochloride		30 mg	30 mg		30 mg	30 mg	30 mg	
Dextromethorphan hydrobromide			10 mg			10 mg	10 mg	10 mg
Doxylamine succinate						6.25 mg		

Table 2: Alka-Seltzer Plus Ingredients and Therapeutic Effects

Combination Ingredients	Therapeutic Effect
Acetaminophen	Pain reliever/Fever Reducer
Chlorpheniramine maleate	Antihistamine
Doxylamine succinate	Antihistamine
Phenylephrine hydrochloride	Nasal Decongestant
Pseudoephedrine hydrochloride	Nasal Decongestant
Dextromethorphan hydrobromide	Cough Suppressant

4.1.1.2 Vanquish®

Vanquish®, an aspirin/acetaminophen/caffeine combination, is indicated for fast, safe, temporary relief of minor aches and pains associated with headaches, colds and flu, backaches, muscle aches, menstrual cramps and minor pain of arthritis. Table 3 outlines the specific ingredient combination responsible for the therapeutic benefits of Vanquish®.

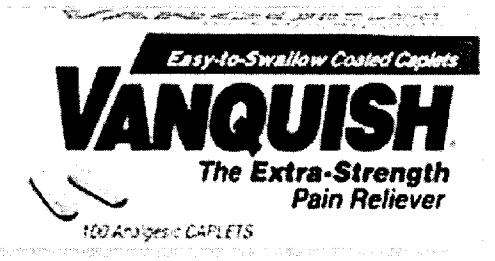


Table 3: Active Ingredients in Vanquish®

Combination Ingredients (Per Tablet)	Vanquish®
Acetaminophen	194 mg
Aspirin	227 mg
Caffeine	33 mg

The efficacy of aspirin and acetaminophen combination products for relief of minor aches and pains has been demonstrated in various studies. On a milligram-to-milligram basis, an aspirin/acetaminophen combination offers equivalent efficacy to the same milligram dose of aspirin or acetaminophen as a single ingredient.

While aspirin and acetaminophen do not have a synergistic effect that offers an enhanced analgesic benefit over single ingredient use (Wallenstein, 1975, Beaver, 1984, Laska, 1984), superiority of aspirin/acetaminophen combinations has been noted when caffeine is a component of the combination product (Hersh, 2000b). In fact, some pain models

show that the addition of caffeine to acetaminophen/aspirin combinations can increase analgesic efficacy by 40-60% (Bach, 1998).

4.1.1.3 Midol®

Midol®, an acetaminophen combination line, provides maximum strength relief of menstrual pain, including cramps, bloating, water-weight gain, headaches, backaches, muscular aches and fatigue. The different formulations of Midol® that contain acetaminophen are outlined in Table 4. As previously noted, the efficacy of acetaminophen is well-established (FDA, 1988; Lipman, 1996), and the addition of caffeine in some formulations can offer a significant adjuvant effect and increase the overall analgesic effect (Bach, 1998). Caffeine and pamabrom, diuretics that are included in some Midol® formulations, are indicated to reduce water weight gain, which reduces breast tenderness and swelling that can accompany the premenstrual and menstrual periods (FDA, 1988). Midol® also contains pyrilamine maleate, an antihistamine which has been shown in controlled clinical trials to enhance analgesic effectiveness (FDA, 1988). The regulatory status of pyrilamine (Category III), however, is currently under FDA review.

Table 4: Active Ingredients in Midol® Products

Combination Ingredients (Per Tablet)	Maximum Strength Midol® Teen	Maximum Strength Midol Menstrual	Maximum Strength Midol PMS
Acetaminophen	500 mg	500mg	500 mg
Pamabrom	25 mg		25 mg
Pyrilamine Maleate		15mg	15 mg
Caffeine		60mg	

4.1.2 General Safety

Analgesic combinations intended for treatment of multiple symptoms are safe products when used according to the package instructions for treatment of the labeled indications.

Combination products are intended to treat a variety of symptoms. While one product may treat several symptoms, it is possible for consumers to inadvertently take multiple

products simultaneously to treat a host of symptoms. Unintentional overdose, which may result from multiple product use, is of concern due to the severity, acute severity and irreversibility, of acetaminophen-induced liver damage.

The risk of using multiple acetaminophen products may be increased in patients treating cold symptoms (fever, cough, or nasal congestion) as well as a headache. Thus, Bayer has capped the dose of each of its acetaminophen containing combination cough/cold/allergy products to provide a maximum of 650 mg per dose, and has enhanced product labeling to warn consumers regarding use of multiple acetaminophen-containing products. Patients taking a medication for menstrual pain are seeking only pain relief and are less likely to take multiple acetaminophen-containing medications.

General safety concerns for combination products containing acetaminophen intended for treatment of multiple symptoms will be addressed below.

4.1.2.1 Combinations Indicated for Multiple Symptoms

It has been suggested that combination products are safest and most beneficial when used to treat two or more of the indicated symptoms. Treatment of a single symptom with a multi-ingredient product may expose consumers to unneeded ingredients (Hersh, 2000b), which increases the potential risk for adverse events. A patient with minor pain, for example, is best treated with a single analgesic and not a combination product. (Hersh, 2000b). Nonetheless, it is important that combination products not be used with other products containing the same ingredients so as to avoid risk of overdose with specific ingredients.

4.1.2.2 Aspirin and Acetaminophen Combinations

Based on their overall safety profiles, aspirin and acetaminophen used in approved combination products do not increase the risk of adverse events as compared to single-ingredient aspirin or acetaminophen (Bach, 1998).

4.1.2.3 Combinations with Caffeine

Combination products containing acetaminophen and aspirin with caffeine have been suggested to be associated with a greater risk of analgesic-associated nephropathy than single agent or combination products containing only aspirin and acetaminophen. Currently available animal and human data, however, do not support the notion that the nephrotoxic risk from aspirin/acetaminophen products is higher than the risk from equal doses of either ingredient taken alone (Bach, 1998). Likewise, there are no epidemiological data to implicate caffeine in nephropathy (Bach, 1998). An apparent elevated risk for nephrotoxic effects due to analgesic combinations may have been suspected because of particular combination products containing phenacetin, an ingredient that is no longer available on the market. In light of the data supporting the

absence of increased risk for kidney damage, it is evident that the distinct therapeutic benefits of aspirin, acetaminophen and caffeine combinations, as found in Vanquish®, outweigh any known risk (Bach, 1998).

Caffeine in analgesic mixtures, while enhancing efficacy, does not increase the potential for analgesic misuse in the general population. Studies have determined that caffeine in such mixtures is no more addictive than other sources of caffeine (Bach, 1998). Therefore, limiting the availability of such caffeine-containing products would not significantly affect the frequency of analgesic abuse/overuse (Bach, 1998).

4.2 Bayer® Aspirin

Aspirin is indicated for both consumer (OTC) and professional uses. As a highly effective pain reliever and antipyretic agent, aspirin can be used safely and effectively under OTC-compliant short-term dosing. Under a physician's guidance, aspirin is indicated for managing cardiovascular events, as well as a variety of inflammatory conditions.

Aspirin, which was first introduced in 1899, has a long history of safe and effective use. Today, over 1 billion tablets are sold yearly. With over 100 years of history of use, aspirin is one of the most extensively studied drugs in the history of medicine. Despite its long history, aspirin is still the focus of current research efforts. Based on such extensive study, the benefits and risks of aspirin are well known.

4.2.1 General Efficacy

Aspirin has been used for over 100 years to relieve pain and reduce fever. Clinical studies demonstrate the efficacy of aspirin as an antipyretic (Yaffee, 1981) and an analgesic at doses ranging from 325 to 1300 mg (Levy, 2002). The efficacy of aspirin has been demonstrated in the relief of various types of pain, including dental, menstrual, post surgical, rheumatoid arthritis and migraine pain (FDA, 1988). Aspirin is also widely recognized for its cardiovascular benefits, as doses ranging from 50 mg – 325 mg have been proven effective in reducing the risk of ischemic stroke and transient ischemic attack (TIA), suspected acute myocardial infarction (MI), preventing recurrent MI, unstable angina pectoris, chronic stable angina pectoris, and for use in some revascularization procedures in selected patients (FDA, 1998). Additionally, aspirin is indicated under professional labeling for relief of the signs and symptoms of rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, spondylarthropathies, and arthritis and pleurisy associated with systemic lupus erythematosus (FDA, 1998). The dosing schedules for each indicated use for aspirin are noted in Table 5. The benefits of various dosing regimens are fully explained in Section 8.4.

Table 5: Benefits of Different Doses of Aspirin

Daily Aspirin Dose	Indication
50-325 mg	Ischemic Stroke and TIA; Suspected Acute MI; Prevention of Recurrent MI; Unstable Angina Pectoris; Chronic Stable Angina Pectoris; CABG; PTCA; Carotid Endarterectomy
325-1000 mg	Mild to moderate pain or fever reduction
3000-4000 mg	Rheumatoid Arthritis; Spondyloarthropathies; Osteoarthritis; Arthritis and Pleurisy of SLE
90-130 mg/kg	Juvenile Rheumatoid Arthritis

As indicated by aspirin's various dosing schedules, aspirin (usually 81 mg or 325 mg/day) is effective in offering cardiovascular protection, while increasing doses offer differing levels of analgesic and anti-inflammatory benefit. The analgesic effects of aspirin follow a dose-response relationship, and therapeutic efficacy is affected by inter-individual pharmacokinetic variation. A single 1000 mg dose, for example, has been found to provide superior relief in some patients over the 650 mg dose, while other consumers achieve satisfactory pain relief with the lower dose (Edwards, 1999). Based on significant individual variation, which is fully discussed in Section 8.4, it is important that consumers not be denied access to the entire range of OTC aspirin doses.

4.2.2 General Safety

Aspirin is one of the oldest and safest pain remedies. As for other drugs, adverse events due to aspirin are dose and duration dependent. Under OTC labeled use, the rate of adverse events does not significantly differ from other OTC analgesics, including acetaminophen. In fact, a retrospective meta-analysis of 3700 patients in 54 single-dose aspirin (325-1300 mg) or acetaminophen (500-2000 mg) dental pain studies found that occurrences of adverse events did not differ from placebo (Cooper, 1985). Likewise, data on the gastrointestinal (GI) safety of OTC analgesics suggest that aspirin and acetaminophen have similar safety profiles when used at single (Cooper, 1985; Elfström, 1999) and multiple (Fries, submitted, 2002) dosing schedules. A comparison of aspirin and acetaminophen safety is presented in Table 6.

Table 6: Safety Comparison Between Aspirin and Acetaminophen

Study/Adverse Event	Dosing (Group Size) Aspirin	Acetaminophen
Single Dose Studies		
Cooper (1985)	325 mg-1300mg (n=927)	500-2000 mg (n=789)
GI Events	Aspirin=Acetaminophen	
CNS Events	Aspirin=Acetaminophen	
Allergy Events	Aspirin=Acetaminophen	
Elfström (1999)	800 mg (n=201)	1000 mg (n=200)
GI Events	Aspirin=Acetaminophen	
Multiple Dose Studies		
Moore (1999)	(n=2900)	(n=2888)
All Adverse Events	Aspirin > Acetaminophen	
Singh, 2000	(n=4164) †	
GI Events	Aspirin > Acetaminophen	
Fries, submitted, 2002†	(n=8816) †	
GI Events	Aspirin=Acetaminophen	

*Statistically significant difference

† Includes patients exposed to prescription and OTC analgesics including aspirin, acetaminophen, ibuprofen or naproxen sodium

As noted, aspirin is associated with an extremely low rate of adverse events at OTC dosing. However, as adverse effects can be associated with duration of use, events occurring with chronic, professional use are often assigned inappropriately to short-term OTC use patterns. Regardless of the indicated use, the benefits of aspirin treatment significantly outweigh the risks (Fries, 1993;Weisman, 2002).

To optimize the benefits and curb any risks associated with aspirin use, current product labeling is designed to inform consumers of relative risks associated with aspirin use and to ensure consumer safety. The Reye's syndrome-warning label on aspirin products, for example, was instated to warn consumers of this risk of aspirin use. Since the initiation of this warning on all salicylate-containing products, there has been a dramatic reduction in the occurrence of Reye's syndrome in the United States (Committee on Infectious Disease, 1982; Belay, 1999). The noted decrease in adverse events due to the warning

has been used to support the importance of ingredient specific labeling. If Reye's syndrome's class labeling were mandated for all analgesic ingredients, the benefit of this warning would be dramatically reduced.

In light of recent concerns regarding acetaminophen safety and the consequent interest in the safety of other analgesic ingredients, the safety of aspirin use is detailed in Section 8.5.

5 SPECIFIC SAFETY CONCERNS AND LABELING RECOMMENDATIONS

While aspirin and acetaminophen are safe ingredients when used according to package instructions, the potential for specific target organ toxicities and the influence of underlying conditions affect the risk of adverse events and warrant caution. Current product labeling addresses these safety concerns; however, in light of the hepatotoxicity risk associated with acetaminophen overdose or its use in conjunction with excessive alcohol, current labeling may need to be modified to ensure safe self-medication with acetaminophen-containing products.

A summary of the main safety concerns associated with aspirin and acetaminophen use is outlined in Table 7, and reviewed below. A more detailed discussion is provided in Section 8.5. Based on safety concerns with individual ingredients, Bayer has take action to introduce product-labeling enhancements to ensure safe product use. Importantly, it should be recognized that Bayer contends that it is not acceptable to take action on *all* ingredients based on risks of *one* ingredient. Broad class labeling is not appropriate for ingredients that have very different pharmacologic properties and different therapeutic benefits and risks.

Bayer contends that it is not acceptable to take action on *all* ingredients based on risks of *one* ingredient.

Table 7: Noteworthy Adverse Events Associated with OTC Aspirin and Acetaminophen Use

Potential Adverse Event	Aspirin	Acetaminophen
Serious Liver Injury		
GI Injury		
Adverse Drug Interactions due to Alcohol		
Adverse Drug Interactions due to Prescription Drugs		

5.1 Hepatic Effects

Acetaminophen use has been associated with permanent hepatic failure, particularly resulting from overdose (intentional or unintentional) or concomitant excessive alcohol use. Recent study data suggest that acetaminophen is the most common cause of drug induced acute liver failure in the United States. In fact, acetaminophen use was indicated in 38% of all liver failure cases reported between January 1998 and October 2000 (Lee, 2001). The association between acetaminophen use and liver failure is not unique to the United States, as acetaminophen is the single most common cause of acute liver failure in Europe and Australia as well (Lee, 2001). The recent data associating acetaminophen use

with hepatotoxicity has prompted concern regarding the general safety of acetaminophen and the scheduling of this FDA review of analgesic safety.

Based on the associated risk between acetaminophen use and hepatotoxicity, Bayer recommends that acetaminophen labeling be enhanced to inform consumers of the specific risks of hepatotoxicity with acetaminophen.

Risk of acetaminophen-induced liver damage increases with excessive dosing as well as alcohol use. The data indicate the need for clear liver-specific warnings in acetaminophen-containing product labeling to ensure safe consumer use. These points will be discussed further in Section 5.4: "Drug Interactions" and Section 5.5" "Overdose Potential".

Unlike acetaminophen, OTC-compliant use of aspirin is associated with an extremely low risk of serious liver effects. Aspirin has rarely been implicated in life-threatening hepatic toxicity. Prescription doses of aspirin have been documented to cause elevations in liver enzymes; however, these increases rarely progress to liver failure with aspirin use (Lewis, 1998). In rare cases, acute, intrinsic hepatic injury has been associated with aspirin use but has not resulted in fulminant liver failure, as has been reported for acetaminophen. Risk of acute hepatotoxicity with aspirin increases with high blood levels of the drug, and is significantly related to pre-existing hepatic impairment, juvenile arthritis, rheumatic fever, or systemic lupus erythematosus (SLE) (Zimmerman, 1990). OTC-compliant use of aspirin, however, is associated with extremely low risk of serious liver effects.

The risk differs greatly between aspirin and acetaminophen with respect to serious hepatotoxicity and therefore necessitates ingredient-specific labeling.

5.2 Gastrointestinal Effects

Aspirin products are currently labeled to reduce the risk of adverse GI effects in susceptible individuals. Because the frequency of GI complaints is increased in individuals with a history of GI illness, aspirin containing product labeling includes the following warning:

Do not take this product if you are allergic to aspirin, have asthma, have stomach problems (such as heartburn, upset stomach or stomach pain) that persist or recur, gastric ulcers or bleeding problems unless directed by a doctor.

FDA has not required similar labeling on acetaminophen-containing products. Based on the mechanism of action, there is reason to believe susceptible populations are at risk for GI problems with acetaminophen use. More recent evidence suggests that GI effects may be associated with all analgesics, including acetaminophen (Rahme, 2000; Stiel, 2000; Garcia-Rodriguez,

GI effects may be associated with *all* analgesics.

2001). Because GI events are commonly attributed to aspirin use, GI events due to other ingredients may be overlooked. Such a recall bias may artificially inflate the apparent number of aspirin-induced GI events. For perspective on relative risks associated with aspirin and acetaminophen use and GI injury, we provide a comprehensive safety overview in Section 8.5: Comprehensive Support of Bayer's Position and Recommendations Safety Overview.

While aspirin used in accordance with OTC labeling does not present a significant risk of severe GI injury, endoscopic studies have implicated OTC-dose/duration-compliant aspirin use in the development of acute superficial lesions suggestive of mucosal injury (Lanza, 1975; Lanza, 1984). However, the clinical significance of these superficial lesions is uncertain, and no correlation to clinical outcome has been demonstrated. Specifically, acute endoscopic changes do not necessarily correlate with risk of bleeding, ulceration, or other untoward effects (Graham, 1986; Bazzoli, 2001). As such, endoscopic findings have very limited value in predicting the frequency or severity of chronic gastric ulcers or gastrointestinal bleeding. In fact, endoscopic findings were not accepted as a meaningful predictor of GI events when the FDA reviewed the approval of COX-2 inhibitors (Arthritis Advisory Committee, 1998).

Serious adverse GI reactions have been reported to occur at an annual rate of 1-2% in individuals who take prescription strength NSAIDs and aspirin regularly (Cryer, 1999). Nonetheless, recent data suggest that the suspected risk of aspirin-induced GI injury, even under such use conditions, has been overestimated, and furthermore that the risks associated with chronic, high dose use has been inaccurately ascribed to short-term OTC use (Singh, 1999).

The risk of developing GI injury due to aspirin is influenced by several factors, including dose and duration of use, use of concomitant medication, increasing age, co-morbid conditions, presence of *H. Pylori* infections and prior history of ulcers or stomach irritation (Halverson, 1999; Bazzoli, 2001).

GI effects attributable to aspirin are overwhelmingly more frequent in patients taking aspirin on a long-term basis. It should be noted that patients with significant bleeding disorders or underlying disease necessitating the use of aspirin (cardiovascular disease or rheumatic diseases) may be at an increased risk for GI disorders or may have an impaired ability to tolerate aspirin-induced gastrointestinal bleeding or other adverse reactions. Although patients with cardiovascular disease may be at increased risk for GI adverse effects due to underlying disease or chronic aspirin use, the benefits of aspirin outweigh the risks (USPTF, 2002). A recent meta-analysis of six trials (6,300 patients), further supporting the favorable benefit-to-risk ratio of aspirin, found that aspirin reduces all cause mortality and that 1-5 deaths can be prevented for every manageable GI event caused (Weisman, 2002).

Misleading advertising by competitors has inappropriately compared the effects of professional, long-term aspirin use to OTC indicated self-use. Some manufacturers argue that aspirin is associated with a large risk of GI injury, and should be avoided in favor of "safer" ingredients, namely, acetaminophen.

Despite recent data supporting the safety of aspirin, many consumers and physicians associate aspirin use with risk of gastrointestinal (GI) side effects, and believe that acetaminophen is a safer analgesic ingredient. This misconception is enhanced by the fact that acetaminophen-containing products are not required to carry GI injury warning, as are aspirin products. Further study is needed to clarify the association of analgesic use and gastrointestinal effects, particularly since previously noted observations may be the result of significant recall bias against the aspirin. GI injury has frequently been ignored when lists of complications and side effects are compiled, and failure to probe for acetaminophen use in GI injury cases may lead to an inaccurate assessment of GI risk.

While it has been purported that acetaminophen is a safe alternative to aspirin as it is associated with a relatively low risk of GI injury, recent data suggest that the relative risk of acetaminophen-induced GI injury may be underestimated. Analysis of the ARAMIS database, a post-marketing surveillance program and the National Arthritis Data Resource, suggests that OTC doses of aspirin and acetaminophen are associated with equal risk of gastrointestinal injury (Fries, submitted, 2002). Furthermore, recent data suggest that daily doses of acetaminophen $\geq$ 2000 mg are associated with increased risk of GI complications similar to NSAIDs, particularly when acetaminophen is taken concomitantly with other NSAIDs (Garcia Rodriguez, 2001; Rahme, 2000). Because chronic use of acetaminophen outside of labeling is common among consumers with osteoarthritis, these data challenge the current paradigm that acetaminophen is associated with minimal risk of GI injury.

In light of recent data associating GI risk with acetaminophen use, epidemiologic data suggest that aspirin is as safe as other analgesic ingredients, including acetaminophen (Fries, submitted, 2002). Despite these data, acetaminophen manufacturers have argued that aspirin products need stronger warnings to inform consumers of the risk of GI injury. Such strengthened labeling has been specifically proposed by acetaminophen manufacturers who fear that more stringent acetaminophen labeling based on concerns of hepatotoxicity will cause consumers to switch away from acetaminophen use to increased aspirin use. They postulate that such a switch would lead to an increased incidence of GI injury. There are no data to support the contention that an increase in consumer awareness regarding potential risks of acetaminophen would cause consumers to switch to aspirin.

5.3 Renal Effects

Renal function is dependent on prostaglandin synthesis, and this is affected by analgesic ingredients. Elevations in blood urea nitrogen or serum creatinine levels have been reported with long-term high dose aspirin (Bonney, 1986), as well as short-term use in patients with underlying renal impairment (Whelton, 1990). Cessation of aspirin use, however, typically results in a reversal of drug-induced effects on renal function (Bonney, 1986; Whelton, 1990).

The risk of analgesic-induced renal toxicity is low; however, some pre-existing conditions may increase the risk. Patients with diabetes (Whelton, 1991), concomitant diuretic therapy, renal or hepatic impairment, cardiac failure, or old age, should use caution with non-prescription analgesic self therapy.

Analgesic nephropathy, a unique type of renal toxicity, has been reported with both aspirin and acetaminophen; however, such toxicity occurs most often only after years of exposure to high therapeutic doses or mixtures containing at least two antipyretic analgesics with caffeine or codeine (De Broe, 1998). Additionally, many early reports of analgesic nephropathy were reported in patients taking large amounts of products containing phenacetin (De Broe, 1998), an ingredient that has been taken off the US market.

5.4 Drug Interaction

The interaction between aspirin or acetaminophen and other drug ingredients may increase the risk of adverse events. Drug interactions that may present serious risk of injury should therefore be addressed in consumer labeling. While important drug interactions are included in aspirin labeling, many such interactions have been left out of the acetaminophen labeling; giving the impression of superior safety in this dimension. The important interactions with respect to the use of acetaminophen and aspirin are summarized below.

5.4.1 Alcohol

The use of alcohol has been implicated as a significant risk factor in acetaminophen hepatotoxicity. The actual incidence of liver toxicity associated with acetaminophen and alcohol, however, is relatively small as compared with exposure, and clinical studies have been presented as evidence of a low risk of liver damage associated with acetaminophen and alcohol use (Dart, 2000; Kuffner, 2001). There are, however, several case reports of severe hepatotoxicity that implicate regular or occasional acetaminophen use with chronic or excessive alcohol use. Thus, editorials and case reports draw attention toward the association between alcohol use and acetaminophen hepatotoxicity and the severity of the drug-induced liver damage.

In recognition of the association between acetaminophen and alcohol use, the FDA has mandated the following alcohol warning on acetaminophen product labels (FDA, 1998):

> *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.*

The FDA has mandated a similar warning on all OTC analgesic-containing products. This current labeling paradigm, which requires nearly identical warnings on all products, greatly misstates the magnitude of the severity of the complications related to each OTC

analgesics, and likely reduces the effectiveness of the warning. Because consumers make judgments on the basis of specific active ingredients (FDA, Aug. 1997), labels that blanket all products together mask the differences between the ingredients. This may lead to inappropriate self-medication decisions and a higher incidence of adverse reactions.

While the current alcohol warning highlights the risk of potential adverse reactions, it falls short in warning consumers of the unique risk of hepatic injury with acetaminophen. The phrasing of information in the alcohol warning influences consumers' perception of the ingredient's risk (FDA, Aug. 1997). FDA warnings are generally designed to contain four elements: a signal word or phase (e.g., "alcohol warning), a statement of dangerous behavior (e.g., "consume 3 or more alcoholic drinks every day"), possible negative outcomes (e.g., liver damage), and a way to remedy the concerns (e.g. "ask your doctor"). The current acetaminophen alcohol warning highlights these key points, stating that people who consume three or more alcohol-containing beverages per day are encouraged to consult their physician before taking the product for self-medication. The association between acetaminophen and liver damage ("*Acetaminophen may cause liver damage.*") in a separate sentence as the alcohol warning, however, does not clearly associate risk of liver damage specifically to alcohol use. Likewise, an analysis of product labeling suggests that quantity-frequency descriptions (e.g., "consume 3 or more alcoholic drinks every day") may not indicate the absolute level of risk presented by a product as consumers tend to believe that they can control their drinking and thereby moderate their risk exposure (FDA, Aug. 1997). Thus, the current alcohol warning may not be sufficient to warn consumers of the unique risk of acetaminophen use with excessive alcohol consumption.

Additionally, the current alcohol warning may encompass a large population of consumers who use alcohol, and may inadequately define the true risk of acetaminophen-induced liver damage. The qualification of 3 drinks per day may define a large sub-segment of people who take OTC analgesic doses safely. Thus, a more precise, authoritative label highlighting the potential risk with alcohol and acetaminophen use is warranted. The American Liver Foundation (ALF, 1998), for example, supports a statement such as the following suggested warning:

Alcohol Warning: If you drink more than 3 alcoholic beverages per day, do not exceed 2 g of acetaminophen per day.

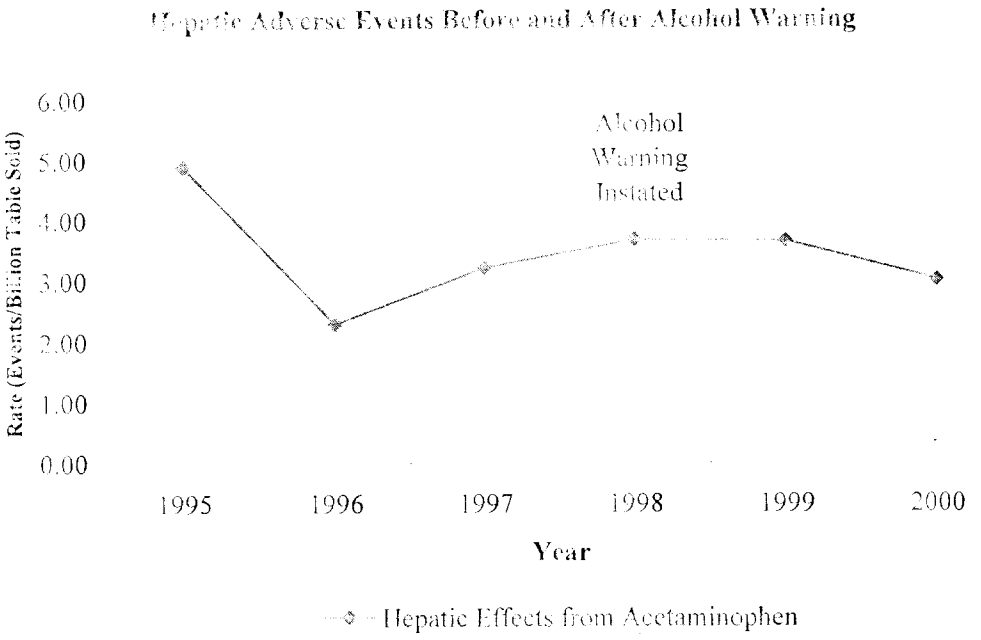
It has been argued that a strengthened alcohol warning on only acetaminophen-containing products would result in consumers switching from acetaminophen to aspirin, thus increasing consumer risk of gastrointestinal events. Therefore, some acetaminophen manufacturers argue for the inclusion of an alcohol warning concerning risk of stomach bleeding with concomitant aspirin and alcohol use as a way to minimize the impact of the important and necessary warning on acetaminophen. Aspirin products, however, are already adequately labeled for GI events and the alcohol warning addresses the issue of concomitant alcohol use with aspirin:

Alcohol Warning: If you consume 3 or more alcoholic drinks every da[illegible] your doctor whether you should take aspirin or other pain relievers/fever reducers. Aspirin may cause stomach bleeding.

Despite FDA action and warnings regarding risk of GI injury with aspirin and alcohol use, the available data (Peura, 1997) require further validation. In fact, the FDA warning concerning concurrent use of alcohol with aspirin was largely based on study data that evaluated the effect of long-term alcohol abuse with aspirin use (Neutel, 2000). Furthermore, competitive interests desirous of maintaining the status quo with respect to analgesic labeling generated much of the data previously presented to the Non-Prescription Drug Advisory Committee. In contrast to the FDA's position, the consensus of the gastroenterology community is that there is not compelling evidence to link moderate concomitant alcohol and NSAID use with increased risk of GI bleeding.

Furthermore, while a manufacturer's contention that alcohol warnings on acetaminophen may increase consumer use of aspirin, there is no evidence to support the notion that specific regulatory action would cause consumers to switch from acetaminophen to aspirin. Additionally, there is no support for the contention that if consumers switched from acetaminophen to aspirin, they would be at a greater risk of injury. As previously stated, aspirin has been shown to be associated with an increased risk of gastrointestinal injury, however the occurrence of serious adverse effects with OTC dosing does not exceed the risk of GI injury due to other OTC analgesics, including acetaminophen (Fries, submitted, 2002). It should also be noted that despite previous FDA regulation regarding alcohol warnings, post-marketing surveillance data do not support a connection between the broad alcohol warning and an overall reduction of adverse events.

Figure 1: Impact of Alcohol Warning on Adverse Events



5.4.2 Prescription Drugs

While all OTC analgesics have been implicated in a number of drug interactions, physicians consider only a few such interactions to be clinically significant. Among the noteworthy drug interactions with aspirin are those associated with concomitant oral anticoagulant, thrombolytic, uricosuric agent, sulfonylurea, corticosteriod or methotrexate use (McEvoy, 2000). Similarly, acetaminophen is associated with adverse drug interactions; however, these are often ignored when discussing acetaminophen safety. Acetaminophen is contraindicated with concomitant anticonvulsant, isoniazid, oral anticoagulant and thrombolytic use (McEvoy, 2000), as these agents may increase the risk of hepatotoxicity (Furey, 1992).

While aspirin and acetaminophen use are contraindicated with particular agents, nearly all the indicated drugs warrant caution with concomitant use, as adverse drug interactions noted with aspirin may also carry risk of interaction with acetaminophen, and vice versa. Side-by-side comparison of drug-interactions between acetaminophen and aspirin, presented in Table 8 and detailed in Section 8.5, suggest that these two ingredients do not differ greatly with respect to adverse drug interactions. Furthermore, while aspirin is contraindicated for concomitant use with certain drugs, aspirin use may in fact be warranted in combination with these drugs under certain conditions (as noted in Table 8).

Table 8: Drug-Drug Interactions with Acetaminophen and Aspirin that Warrant Caution

Prescription Drug	Acetaminophen	Aspirin
Oral Anticoagulants and Heparin	+	+*
Anti-thrombotics	+	+
Anti-convulsants	+	+
Uricosuric Agents	+	+
Corticosteroids	+	+
Methotrexate	O	+**
Isoniazid	+	O
Sulfonylureas	O	+***
Zidovudine	+	O

+ = Drug-drug interaction requires caution due to inherent risk of adverse event

O = Drug-drug interaction presents minimal risk of serious adverse event

*Despite the interaction between aspirin and heparin use, the American College of Cardiology and American Heart Association promotes the use of aspirin and heparin for management of patients with acute coronary syndrome (unstable angina) (Ryan, 1999)

**Aspirin administration to patients receiving low dose methotrexate therapy for treatment of rheumatic conditions is of little safety concern (Haas, 1999).

***Despite potential interactions between some anti-diabetic drugs and aspirin, the American Diabetes Association (ADA) advocates the benefits of aspirin, particularly for use as a primary prevention strategy in men and women with diabetes who are at high risk for cardiovascular events (American Diabetes Association, 2002).

5.4.3 Other Over-the-Counter Analgesics

OTC analgesic products are safe and effective when taken alone, however concomitant use of more than one product may be associated with drug interactions that increase the risk for adverse events or decrease efficacy.

Concomitant use of aspirin or acetaminophen with other OTC analgesic ingredients, including the NSAIDs, may increase risk of gastrointestinal (Garcia-Rodriquez, 2001; Rahme, 2000) or renal disorders (McEvoy, 2000). The potential increased risk for GI and renal adverse events warrant caution with concomitant use of aspirin, ibuprofen, naproxen sodium or ketoprofen with each other or prescription NSAIDs.

The efficacy of low-dose aspirin used for cardiovascular benefit may be compromised by concomitant use of aspirin with other NSAIDs. Treatment with ibuprofen in patients with increased cardiovascular risk may limit the cardioprotective effects of aspirin (Catella-

Lawson, 2001). Currently, there is no product labeling that warns consumers of this risk. Due to the potential life-threatening effect of decreased cardioprotection, consumers should be made aware of this potential interaction.

5.5 Overdose Potential

With the wide variety of aspirin and acetaminophen products available for treatment of a variety of conditions, including headache, pain and fever or cold, muscle aches and pains, menstrual pain, toothache pain, pain with sleeplessness, allergy and sinus pain, heartburn and arthritis, consumers are at potential risk for self-medicating with multiple products. Concern has been raised over multiple products and the corresponding excessive exposure to analgesics. Acetaminophen overdose due to dosing with multiple products may result in life-threatening liver damage. Aspirin does not have the same overdose concerns.

Despite the wide availability of products containing analgesic ingredients, the overall incidence of adverse events with proper OTC use is low, particularly considering the enormous volume of drug use (Prescott, 2000). While overdose may occur for a variety of reasons, as detailed in Section 8.5, recent reports suggest that acetaminophen is the most common cause of total acute liver failure in the US (Lee, 2001), as a result of accidental or intentional overdose. Accidental misuse of acetaminophen is responsible for more morbidity and mortality than intentional overdose (attempted suicide), despite the fact that larger acetaminophen doses are usually taken during intentional overdosing situations (Schiodt, 1997).

Accidental overdose of acetaminophen raises special concern since symptoms of overdose, including nausea, vomiting, diaphoresis, and general malaise, do not present until 24 – 48 hours after drug overdose. In contrast, symptoms of aspirin overdose, including nausea, vomiting, tinnitus, hyperthermia and hyperventilation, are typically recognized within three to four hours of ingestion.

After overdose, particularly unintentional or accidental overdose, patients are prompted to seek medical care once symptoms arise, as physical indicators are the first sign of overdose. Acetaminophen overdose can be successfully treated with an antidote, N-acetylcysteine, however, treatment is most effective immediately following overdose, when symptoms are not yet apparent. Unfortunately, once symptoms present following acetaminophen overdose, permanent liver damage may be already inevitable. Symptoms of aspirin overdose, on the other hand, are generally reversible and treatable with palliative care.

The potential for life-threatening acetaminophen overdose is largely dependent on the dose of the drug taken. To address concern of possible multiple product use and consequent overdosing above the approved acetaminophen limit, Bayer has voluntarily capped the acetaminophen dose in its cough/cold/allergy products to deliver no more than 650 mg per dosing occasion. This precautionary measure is intended to reduce the

potential for overdose under conditions in which other products might be used simultaneously with other acetaminophen containing products.

To further protect consumers from unsafe dosing and self-medication practices, Bayer supports labeling all acetaminophen-containing products with strengthened warnings admonishing consumers of the risks of taking multiple acetaminophen-containing products simultaneously.

Based on the toxic potential of acetaminophen some advocates for drug safety support the use of package-size limitations as a means of reducing the incidence of acetaminophen toxicity and overdose (Gunnell, 2000). In fact, national policies regarding acetaminophen package-size limitations have been implemented in some countries, including the United Kingdom. While some data suggest that package size limitations may affect the incidence of hepatotoxicity from acetaminophen overdose (Hawton, 2001), a recent study suggests that reduced acetaminophen availability will increase poisoning with alternative analgesics while not affecting incidence of acetaminophen poisoning (Balit, 2002). Likewise, it has been suggested that a restriction in package size will not affect the incidence of severe acetaminophen overdose resulting in liver failure (Robinson, 2000).

Should package restrictions be instated on acetaminophen-containing products, it is unlikely that similar restrictions on aspirin or NSAID packaging would affect the rate of NSAID or aspirin mortality, as overdose with aspirin or NSAIDs result in vomiting and other symptoms that encourage consumers to seek medical attention. Additionally, the inconvenience caused by package limitations may adversely affect consumers of aspirin who require daily aspirin for cardiovascular prevention.

5.6 Allergy

Some patients with asthma may experience potentially life-threatening hypersensitivity reactions to aspirin (Settipane, 1983). Although the mechanism of aspirin intolerance is unknown, patients with a history of nasal polyps or severe rhinitis, sinusitis, urticaria, angioedema, bronchospasm, or anaphylaxis associated with aspirin use, should avoid aspirin.

In light of the potential hypersensitivity reactions with aspirin use, the following labels are included on aspirin-containing products:

Do not use if you are allergic to aspirin or any other pain reliever/fever reducer.

While acetaminophen is often recommended as an alternative treatment for aspirin-sensitive patients, sensitivity has been reported in as many as 34 percent of aspirin-sensitive asthma patients receiving average doses of acetaminophen (Settipane, 1995). The reported hypersensitivity reaction to acetaminophen is generally not as severe as the aspirin-induced reaction (Settipane, 1995). Clearly, however, asthma sensitization is not unique to aspirin. In fact, like aspirin, acetaminophen has been associated with allergy,

anaphylaxis, urticaria, asthma and bronchospasm, rashes, and rarely, Stevens Johnson syndrome. A comparative clinical study of acetaminophen and aspirin suggests that patients experience skin irritation and burning, watery eyes more often with acetaminophen use than with aspirin or placebo treatment (Cooper, 1985). Allergic reactions with acetaminophen should also be considered, as the favorable use of acetaminophen over aspirin in children may be a contributing factor to the increasing prevalence of asthma, atopic eczema, and allergic rhinitis in children of Western countries, including the United States (Varner, 1998). This hypothesis is based on the biologic effects of cytokines and prostaglandins on allergic sensitization and the differing mechanism of action of aspirin and acetaminophen (Varner, 1998).

6 CONCLUSIONS

The Bayer Corporation is committed to providing the public with safe products that offer therapeutic relief of pain and other symptoms that commonly affect the public on a daily basis. When used according to package instructions, Bayer's OTC analgesic products are safe and effective. Bayer contends that consumers are able to make wise self-medication decisions through use of product labeling. Proper labeling, therefore, allow consumers to reduce their risk of adverse events.

In light of recent concerns regarding the potential risk of acetaminophen and serious liver damage, Bayer supports regulatory action to protect consumers from risk of overdose. Enhanced ingredient-specific labeling, for example, may inform consumers of relative risks and allow for educated self-medication regimens. To this point, Bayer promotes product labeling that warns consumers of the dangers of using multiple acetaminophen-containing products or concomitant alcohol.

While enhanced product labeling and dose restriction for acetaminophen may reduce consumer risk of serious liver toxicity, similar action on aspirin products based on broad, class regulations would not achieve any benefit. The risk of serious hepatotoxicity has been associated only with acetaminophen, and potential adverse events related to aspirin are already adequately outlined in product labels (Reye's syndrome and GI bleeding). Thus, additional warnings on aspirin-containing products are not warranted. Importantly, the addition of inappropriate warnings or restrictions on aspirin products could negatively impact doctor recommended aspirin use. Because aspirin confers important cardiovascular benefits, inappropriate labeling could have a significant impact on cardiovascular/all cause mortality, thus adversely impacting public health.

Enhanced labeling on acetaminophen products, without additional regulation on aspirin products, would highlight for consumers the potential risks of acetaminophen without confusing consumers as to risks with other OTC ingredients. Because OTC products are safe when used according to package restrictions, it is unlikely that additional warnings on acetaminophen products would put consumers at increased risk of adverse events should they switch from a product containing acetaminophen to another OTC analgesic ingredient.

7 RESPONSES TO QUESTIONS POSED TO THE COMMITTEE

The FDA will propose a number of questions regarding possible actions to enhance analgesic safety. These questions may consider regulatory action on combination products, dosing, labeling and packaging restrictions.

This table highlights some key questions that may be raised during the NDAC discussion of regulatory action to ensure safe use of acetaminophen and aspirin. With respect to acetaminophen, questions will be directed to hepatotoxicity; with respect to aspirin questions will be directed to gastrointestinal effects.

Table 9. Bayer's Position on Questions Regarding Specific Regulatory Actions to Ensure Safe Product Use

Combination Products	*Acetaminophen*	*Aspirin*
Should OTC combination products be reformulated to eliminate Acetaminophen?	**Should be reviewed and discussed** OTC combination products containing acetaminophen are not significantly involved in unintended liver injury or fatalities from acetaminophen. *RX combination* products and OTC single-ingredient products are responsible for majority of unintended liver injury and for overall fatalities from acetaminophen. (FDA briefing information)	There are very few OTC aspirin combination products in the market. Use is often self-limited because of indication and effect of other active ingredients. Aspirin combination products not significantly involved in reported cases of gastrointestinal toxicity and the consequence of an acute overdose is generally less severe.

Dosing	*Acetaminophen*	*Aspirin*
Should the amount of acetaminophen per dosage unit be limited (i.e., eliminate Extra-Strength [500 mg and 650 mg] dose forms)? **Should similar action be taken with aspirin products (i.e., eliminate Extra-Strength doses)?**	**Should be reviewed and discussed** Incidence and severity of liver injury with acetaminophen is dose-related. 500-mg acetaminophen-containing products appeared to be most implicated in FDA review of US cases of liver injury. (FDA briefing information)	Most cases of GI toxicity from aspirin are patients taking aspirin at doses of less than or equal to 325 mg per day as part of a long-term RX regimen for cardiac or cerebrovascular indications under physician supervision. Higher dose strengths are required for efficacy in OTC pain or fever indications, e.g., migraine. OTC use pattern is episodic and not long-term.

Labeling	*Acetaminophen*	*Aspirin*
Should the FDA require more explicit OTC label warnings regarding the potential for cross dosing (e.g., "This product contains acetaminophen. Do not use with any other products containing acetaminophen. Your total daily dose of acetaminophen should not exceed 2000 mg per day.")	**Should be reviewed and discussed** Bayer supports inclusion of a liver specific warning on acetaminophen-containing products as well as strengthened warnings on the hazards of taking multiple acetaminophen products simultaneously. Lowering the daily dose limit should be discussed. Hepatotoxicity is dose-related and may occur at doses less than 4 grams/day.	There are few aspirin combination products on the market, and cross dosing with aspirin-containing products is rare. Most cases of GI toxicity associated with aspirin are at doses less than or equal to 325-mg daily as part of a long-term RX regimen for cardiovascular or cerebrovascular disease. Higher dose strengths are required for efficacy in OTC pain and fever indications. Use pattern is episodic and not long-term for OTC indications.

Labeling	*Acetaminophen*	*Aspirin*
Should the FDA strengthen the label regarding liver toxicity; provide information regarding conditions and situations that may increase the risk of liver toxicity (e.g., alcohol use and abuse, underlying liver disease, certain co-medications, chronic under-nutrition, prolonged fasting)? **Should FDA do the same with GI toxicity associated with aspirin?**	**Should be reviewed and discussed** Bayer supports a liver-specific warning on all acetaminophen products. Alcohol , underlying liver disease, and some medications were potential contributing factors in FDA case series of liver injury from acetaminophen (FDA briefing information)	Aspirin OTC products are already responsibly labeled to warn consumers to ask a doctor before use "if you have stomach problems (such as heartburn, upset stomach, [illegible]tomach pain) that continue or come back, bleeding problems, ulcers." and include other appropriate warnings. Most cases of GI bleeding associated with aspirin occur in patients taking aspirin for cardiovascular indications under physician supervision. (FDA briefing information)
Packaging	*Acetaminophen*	*Aspirin*
Should the FDA limit the number of acetaminophen doses per package or require a blister pack configuration? **Should similar limitations regarding blister packing and the number of doses per package be applied to aspirin?**	**Should be reviewed and discussed** Acetaminophen overdose is the most common cause of acute liver failure in the US (Of these cases approx. 60 % accidental 40 % suicide.) Accidental toxicity occurs when patients consume larger than recommended amounts for pain relief. Limiting package size may prevent cases (Lee, 2001).	Episodic high doses are not implicated in GI toxicity associated with aspirin. Packaging restrictions may be a hardship for elderly persons taking aspirin for cardiovascular or cerebrovascular indications or inflammatory arthritis under a physician's care.

8 COMPREHENSIVE SUPPORT OF BAYER'S POSITION AND RECOMMENDATIONS

8.1 REGULATORY HISTORY

The Internal Analgesic, Antipyretic and Antirheumatic Drug Products for Over-the-Counter Human Use; Tentative Final Monograph (FDA, 1988), issued by the Food and Drug Administration (FDA), establishes proposed conditions under which over-the-counter (OTC) analgesic, antipyretic and antirheumatic drugs products are generally recognized as safe and effective. The Tentative Final Monograph (TFM) establishes approved active ingredients, dosing regimens, and permissible combinations of active ingredients, as well as labeling requirements for such products.

The TFM, issued on November 16, 1988, evolved from an advanced notice of proposed rulemaking in 1977. Comments on the proposed rulemaking regarding OTC internal analgesic, antipyretic, and antirheumatic drug products were accepted until February 1978. In March 1980, the agency advised that it had reopened the administrative record to allow for consideration of data and information that had been filed after February 1978. The agency opened the comment period until March 21, 1980. In response to the advance notice of proposed rulemaking for OTC internal analgesic, antipyretic, and antirheumatic drug products, the FDA received comments from trade associations, drug manufacturers, health professionals and health professional associations, a drug-standard-setting association, a health foundation, and a consumer group as well as a numerous individual consumers.

While the TFM details use conditions for a variety of OTC analgesic ingredients, this section reviews only the various rulemakings pertinent to aspirin and acetaminophen with respect to warnings and contraindications for use. Additionally, we provide an overview of how aspirin and acetaminophen product labeling has evolved over time.

8.1.1 Aspirin/Acetaminophen Dosing

Based on comments received and the FDA guidance committee's review, the TFM provides regulatory substantiation for labeled directions for use and dosing on the currently marketed 500 mg aspirin product. The FDA made recommendations on aspirin and acetaminophen dosing based on minimum effective and maximum daily doses, as outlined in Table 10

At the time the dosing recommendations were proposed the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Drug Products raised concern that the existence of many different products that vary in the amount of aspirin per dosage unit could lead to consumer confusion. Thus, the proposed dosing recommendations were based on the established minimum effective dose for adults (standard dosing: 325 mg per dosage unit) for aspirin and acetaminophen products. Nonstandard products, which

contain more than 325 mg but less than 650 mg per unit, are included under the recommended "nonstandard" dosing schedule. Additionally, the Advisory Review Panel established an hourly rate limitation of 167 mg/hour for adults, and established 4000 mg as the maximum daily dosage for "standard" drugs (aspirin, acetaminophen and sodium salicylate). It was deemed that dosing regimens exceeding the recommended maximum hourly or daily limit are associated with a greater risk of toxicity and are not associated with a greater therapeutic benefit.

Table 10: Dosing Recommendations for Aspirin and Acetaminophen

	Aspirin	Acetaminophen
Standard Schedule	325 mg to 650 mg every 4 hours not to exceed 3900 mg in 24 hours	325 mg to 650 mg every 4 hours not to exceed 3900 mg in 24 hours
Nonstandard Schedule	325 mg to 975 mg initially followed by 650 mg every 4 hours not to exceed 3900 mg in 24 hours	325 mg to 975 mg initially followed by 650 mg every 4 hours not to exceed 3900 mg in 24 hours
Other Dosing Schedules	325 mg to 842 mg initially followed by 421 mg every 3 hours not to exceed 3789 mg in 24 hours	500 mg to 1000 mg initially followed by 500 mg every 3 hours or 1000 mg every 6 hours not to exceed 4000 mg in 24 hours
	421 mg to 970 mg initially followed by 421 to 485 mg every 4 hours or 842 mg to 970 mg every 6 hours not to exceed 3880 mg in 24 hours	
	485 mg to 1000 mg initially followed by 485 mg to 500 mg every 3 hours or 970 mg to 1000 mg every 6 hours not to exceed 4000 mg in 24 hours	
	500 mg to 650 mg every 4 hours not to exceed 3900 mg in 24 hours	

Based on comments and data submitted to the FDA, the agency concluded in 1988 that because aspirin and acetaminophen are indicated for the same OTC uses, and have been extensively promoted as comparable ingredients, it is reasonable for aspirin dosing

intervals to correspond with acetaminophen dosing intervals (FDA, 1988). Despite this conclusion, the FDA failed to cite clinical substantiation for the recommended aspirin dosing regimen which s not the standard approved schedule (1 gram every 6 hours, not to exceed 4 grams in 24 hours).

8.1.2 Professional Labeling

Aspirin is indicated for use under physician guidance for treatment of rheumatologic diseases and cardiovascular protection. Acetaminophen, on the other hand, is not indicated for these uses and does not have professional labeling.

8.1.2.1 Rheumatologic Diseases

The Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Drug Products noted that aspirin dose regimens less than 4000 mg per day for a limited period of time (7-10 days) may be lower than the optimal adult daily dosage required for anti-inflammatory effect in patients with rheumatoid arthritis. It was further emphasized that only a physician can individualize the salicylate dosage needed for optimal anti-inflammatory effectiveness. Thus, it was concluded that aspirin is safe for use as an OTC antirheumatic under the advice and supervision of a physician. The TFM of 1988 and the Final Rule for Professional Labeling of Aspirin, Buffered Aspirin, and Aspirin in Combination with Antacid Drug Products, established in 1998, upheld the professional labeling for aspirin for treatment of rheumatologic diseases.

According to the Final Rule for Professional Labeling of Aspirin, aspirin is indicated under professional labeling for relief of the signs and symptoms of rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, spondylarthropat[illegible]s, and arthritis and pleurisy associated with systemic lupus erythematosus (FDA, 1988).

Under its professional labeling, the Advisory Review Panel recommended an initial aspirin dose of 3 gram/day in divided doses, with increased doses as needed for anti-inflammatory efficacy with target plasma salicylate levels of 150-300 µg/ml (FDA, 1998). This dosing recommendation, which is supported by the Arthritis Foundation, suggests that some patients may safely take more than 3 grams of aspirin per day provided that gastrointestinal symptoms, loss of auditory acuity or tinnitus does not occur.

8.1.2.2 Cardiovascular Protection

The FDA also proposed professional labeling for the use of aspirin in the secondary prevention of recurrent transient ischemic attacks (TIAs) and myocardial infarction (MI) in the TFM (1988). In describing the proposed professional labeling, the FDA provided detailed information regarding the specific indication, clinical trials, precautions, adverse reactions, and dosage and administration for TIA and MI prevention (FDA, 1988).

In 1996, the FDA proposed to amend the professional labeling to include information on the use of aspirin, buffered aspirin, and aspirin in combination with antacid to reduce mortality in people with suspected acute MI (FDA, 1996).

In 1998, the Final Rule for Professional Labeling of Aspirin, which includes full prescribing information for the professional uses of aspirin, was established. According to this rule, low dose aspirin is indicated for reducing the risk of ischemic stroke and transient ischemic attack (TIA), suspected acute myocardial infarction (MI), preventing recurrent MI, unstable angina pectoris, chronic stable angina pectoris, and for use in some revascularization procedures in selected patients (FDA, 1998).

8.1.3 Alcohol Warning

In 1977, the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Drug Products found evidence of possible synergies between alcohol and analgesic use. In particular, the panel reviewed data on aspirin and gastrointestinal bleeding (Astley, 1967; Needham, 1971) and considered data on the metabolism of acetaminophen in the presence of various types of liver disease, including alcoholic liver cirrhosis. At the time of that data review, no recommendations were made regarding a warning for use of aspirin or acetaminophen with alcohol.

In establishing the TFM in 1988, the FDA did not receive any comments concerning earlier discussions about a possible synergy between alcohol and aspirin with regard to cause gastrointestinal bleeding, or the absence of its mention in labeling. The FDA did, however, receive several comments expressing concern that drugs that induce microsomal enzyme activity, such as alcohol, may increase the potential for acetaminophen-induced hepatotoxicity. After reviewing comments and data submitted to the FDA concerning alcohol use and risk of acetaminophen-induced hepatotoxicity, the FDA determined that the data were insufficient to warrant a label against the use of OTC acetaminophen products with alcohol. However, the FDA remained open to reviewing additional data that might demonstrate the need for revised labeling (FDA, 1988).

Following the establishment of the TFM, the FDA received one comment in support of labeling revisions concerning the use of alcohol and acetaminophen, and two comments in opposition to such labeling revisions. Because the data received were contradictory, the FDA convened a meeting of the Non-prescription Drugs Advisory Committee in June 1993 to review the current data and the need for an alcohol warning for OTC drug products containing acetaminophen. In addition to reviewing whether the data supported the need for an alcohol warning, the Advisory Committee considered the population at risk for alcohol-related acetaminophen toxicity and the benefit-to-risk ratio of other OTC analgesic/antipyretic agents. Based on this review, the committee was given the task to determine whether or not an alcohol warning was warranted, and if so, what types of information should be included in such labeling.

Throughout the meeting of the Advisory Committee, published case reports of acetaminophen-induced liver toxicity in alcohol abusers, data on pharmacokinetics of

acetaminophen metabolism in alcoholics, epidemiologic data and a series of animal studies were reviewed. Additionally, the American Liver Foundation, and consultants from Whitehall Labs and McNeil Consumer Products, who displayed different views on the risks of alcohol use and OTC drug use, addressed the Committee. While the American Liver Foundation and Whitehall Labs emphasized the need to educate health professionals and consumers about the potential risks of acetaminophen and alcohol, McNeil representatives focused on raising concern regarding consumers switching from acetaminophen to alternative OTC analgesics associated with gastrointestinal toxicity, (e.g., aspirin). McNeil representatives stressed that acetaminophen-related hepatotoxicity is a rare event as compared to gastrointestinal bleeding associated with other OTC analgesic products (e.g., non-steroidal anti-inflammatory drugs (NSAIDs)). They purported that more cases of serious toxicity would result from a stringent warning on acetaminophen and consumers switching from acetaminophen to other NSAIDs (Summary minutes from the June 29, 1993 meeting of the Non-prescription Drugs Advisory Committee).

After considering all the available data, the Non-prescription Drugs Advisory Committee concluded that alcohol abusers or heavy drinkers are at increased risk for developing liver toxicity when using acetaminophen, and an alcohol warning was therefore warranted. Based on concerns raised by McNeil, the Committee concluded that an alcohol warning on OTC drug products containing acetaminophen, in the absence of a similar warning on products containing other internal analgesic/antipyretic ingredients, would cause alcohol users to switch to product containing other ingredients that may have equivalent or greater risks. The Committee recommended that an alcohol warning aimed to advise alcoholics or heavy drinkers of the risks of concomitant acetaminophen use be placed on acetaminophen OTC products. However, the Committee supported implementation of such a warning only after fair consideration of whether similar warnings were needed on other analgesics (Summary minutes from the June 29, 1993 meeting of the Non-prescription Drugs Advisory Committee).

In a Joint Meeting of the Non-prescription Drugs Advisory Committee and Arthritis Advisory Committee in September 1993, the FDA reviewed the risks associated with aspirin or other NSAID use by heavy alcohol users or abusers. Considering unpublished data with methodological flaws submitted by McNeil Consumer Products, both Committees jointly concluded that the use of aspirin and other NSAIDs increases the risk of upper gastrointestinal bleeding in heavy alcohol users or abusers. Thus, implementation of an alcohol warning was recommended (Summary minutes from the September 8, 1993 meeting of the Non-prescription Drugs Advisory Committee).

In 1997, after consideration of comments submitted to the FDA following the September 1993 Joint Advisory Committee Meeting, the FDA issued a notice of proposed rulemaking that would establish alcohol warnings for all OTC drug products containing internal analgesic/antipyretic active ingredients labeled for adult use (FDA, Nov. 1997). With regard to acetaminophen, the FDA determined that individuals with a history of heavy alcohol use or abuse have an increased risk of hepatotoxic effects of acetaminophen. With regard to aspirin and other OTC analgesic products, the FDA noted

that the available data raised *logical* concern of a potential increased risk of gastrointestinal bleeding in individuals with a history of heavy alcohol use or abuse, thus warranting an alcohol label. However, while both the irritant effects of alcohol and the separate effects of aspirin on the gastric mucosa are well documented, the FDA acknowledged that the available data did not provide sufficient information to assess the magnitude of the risk of aspirin use by heavy alcohol users or abusers.

In response to the proposed rulemaking for requirement of an alcohol warning, the FDA received two comments arguing that the warning was not based on sound scientific evidence. The FDA disagreed, suggesting that the risk of aspirin or alcohol use and gastrointestinal bleeding is well established, and that while the data differ as to the exact magnitude of the increased risk associated with the combined use of aspirin (or other NSAIDs) and routine heavy alcohol use, it was unnecessary to demonstrate precisely how much the risk is increased in order to require an alcohol warning (FDA, 1998).

8.2 CURRENT PRODUCT LABELING

Full product labeling, which is included in every package and can be found in the Physicians Desk Reference (PDR) manual, provides consumers with information on product ingredients (active and inactive), indications and directions for use, warnings and how the product is supplied. The information in these labels is strictly regulated by the FDA as outlined in the Internal Analgesic, Antipyretic and Antirheumatic Drug Products for Over-the-Counter Human Use; Tentative Final Monograph (TFM) (FDA, 1988)

There is a clear lack of proportionality between the FDA-mandated labeling for acetaminophen and aspirin. Aspirin-containing products, for example, are required to have prominent warnings highlighting the risk of Reye's syndrome, alcohol use and risk of GI injury, use during pregnancy, and potential adverse drug-interactions. Acetaminophen products, however, have a prominent alcohol warning concerning risk of liver injury, but lack extensive labeling parallel to aspirin's label.

The current acetaminophen label fails to adequately highlight the risks associated with acetaminophen overdose. While the label notes that acetaminophen should not be used "with any other product containing acetaminophen," it fails to warn consumers of the specific risks associated with multiple product use. In an effort to highlight these risks associated with multiple acetaminophen-containing product use, Bayer has voluntarily revised its labeling on its acetaminophen containing products (Alka-Seltzer Plus®; Midol®; Vanquish®. This revision was largely based on studies suggesting that a consumer's perception of risk is enhanced by specific disclosures rather than general descriptors (Morris, 1989).

The current product labeling for Bayer's aspirin and acetaminophen-containing products, as well as current labeling for single-ingredient acetaminophen products are provided below.

8.2.1 Bayer Aspirin® Product Labeling

Active Ingredient

325 mg

Inactive Ingredients

Cellulose, Hypromellose, Starch, Triacetin

Indications

For the temporary relief of: headache, menstrual pain, muscle pain, pain and fever of colds, toothache, minor pains of arthritis.

Directions

Drink a full glass of water with each dose

Adults and children 12 years and over: take 1or 2 caplets every 4 hours not to exceed 12 caplets in 24 hours.

Children under 12 years: consult a doctor

Warnings

Reye's syndrome: Children and teenagers should not use this medicine for chicken pox or flu symptoms before a doctor is consulted about Reye's syndrome, a rare but serious illness reported to be associated with aspirin.

Do not use if you are allergic to aspirin or any other pain reliever/fever reducer.

Ask a doctor before use if you have stomach problems (such as heartburn, upset stomach, or stomach pain) that continue or come back, bleeding problems, ulcers, or asthma.

Stop use and ask a doctor if: an allergic reaction occurs. Seek medical help right away; Pain gets worse or lasts for more than 10 days; redness or swelling is present; fever lasts for more than 3 days; new symptoms occur; or if ringing in the ears or loss of hearing occurs.

If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use aspirin during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Alcohol Warning

If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take aspirin or other pain relievers/fever reducers. Aspirin may cause stomach bleeding.

Drug Interaction Precaution

Ask a doctor or pharmacist before use if you are taking a prescription drug for anticoagulation (blood thinning), gout, diabetes, or arthritis

8.2.1.1 Professional Aspirin Labeling

Indications

Vascular Indications (Ischemic Stroke, TIA, Acute MI, Prevention of Recurrent MI, Unstable Angina Pectoris, and Chronic Stable Angina Pectoris): Aspirin is indicated to: (1) Reduce the combined risk of death and ischemic stroke or transient ischemia of the brain due to fibrin platelet emboli, (2) reduce the risk of vascular mortality in patients with a suspected acute MI, (3) reduce the combined risk of death and nonfatal MI in patients with a previous MI or unstable angina pectoris, and (4) reduce the combined risk of MI and sudden death in patients with chronic stable angina pectoris.

Revascularization Procedures (Coronary Artery Bypass Graft (CABG), Percutaneous Transluminal Coronary Angioplasty (PTCA), and Carotid Endarterectomy): Aspirin is indicated in patients who have undergone revascularization procedures (i.e., CABG, PTCA, or carotid endarterectomy) when there is a preexisting condition for which aspirin is already indicated.

Rheumatologic Disease Indications (Rheumatoid Arthritis, Juvenile Rheumatoid Arthritis, Spondyloarthropathies, Osteoarthritis, and the Arthritis and Pleurisy of Systemic Lupus Erythematosus (SLE)):Aspirin is indicated for the relief of the signs and symptoms of rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, spondyloarthropathies, and arthritis and pleurisy associated with SLE.

Dosage and Administration

Each dose of aspirin should be taken with a full glass of water unless patient is fluid restricted. Anti-inflammatory and analgesic dosages should be individualized. When aspirin is used in high doses, the development of tinnitus may be used as a clinical sign of elevated plasma salicylate levels except in patients with high frequency hearing loss.

Ischemic Stroke and TIA: 50-325 mg once a day. Continue therapy indefinitely.

Suspected Acute MI: The initial dose of 160-162.5 mg is administered as soon as an MI is suspected. The maintenance dose of 160-162.5 mg a day is continued for 30 days post-infarction. After 30 days, consider further therapy based on dosage and administration for prevention of recurrent MI.

Prevention of Recurrent MI: 75–325 mg once a day. Continue therapy indefinitely.

Unstable Angina Pectoris: 75–325 mg once a day. Continue therapy indefinitely.

Chronic Stable Angina Pectoris: 75–325 mg once a day. Continue therapy indefinitely.

CABG: 325 mg daily starting 6 hours post-procedure. Continue therapy for 1 year post-procedure.

PTCA: The initial dose of 325 mg should be given 2 hours pre-surgery. Maintenance dose is 160–325 mg daily. Continue therapy indefinitely.

Carotid Endarterectomy: Doses of 80 mg once daily to 650 mg twice daily, started presurgery, are recommended. Continue therapy indefinitely.

Rheumatoid Arthritis: The initial dose is 3 g a day in divided doses. Increase as needed for anti-inflammatory efficacy with target plasma salicylate levels of 150–300 mg/mL. At high doses (i.e., plasma levels of greater than 200 mg/mL), the incidence of toxicity increases.

Juvenile Rheumatoid Arthritis: Initial dose is 90–130 mg/kg/day in divided doses. Increase as needed for anti-inflammatory efficacy with target plasma salicylate levels of 150–300 mg/mL. At high doses (i.e., plasma levels of greater than 200 mg/mL), the incidence of toxicity increases.

Spondyloarthropathies: Up to 4 g per day in divided doses.

Osteoarthritis: Up to 3 g per day in divided doses.

Arthritis and Pleurisy of SLE: The initial dose is 3 g a day in divided doses. Increase as needed for anti-inflammatory efficacy with target plasma salicylate levels of 150–300 mg/mL. At high doses (i.e., plasma levels of greater than 200 mg/mL), the incidence of toxicity increases.

Contraindications

Allergy: Aspirin is contraindicated in patients with known allergy to nonsteroidal anti-inflammatory drug products and in patients with the syndrome of asthma, rhinitis, and nasal polyps. Aspirin may cause severe urticaria, angioedema, or bronchospasm (asthma).

Reye's Syndrome: Aspirin should not be used in children or teenagers for viral infections, with or without fever, because of the risk of Reye's syndrome with concomitant use of aspirin in certain viral illnesses.

Warnings

Alcohol Warning: Patients who consume three or more alcoholic drinks every day should be counseled about the bleeding risks involved with chronic, heavy alcohol use while taking aspirin.

Coagulation Abnormalities: Even low doses of aspirin can inhibit platelet function leading to an increase in bleeding time. This can adversely affect patients with inherited (hemophilia) or acquired (liver disease or vitamin K deficiency) bleeding disorders.

GI Side Effects: GI side effects include stomach pain, heartburn, nausea, vomiting, and gross GI bleeding. Although minor upper GI symptoms, such as dyspepsia, are common and can occur anytime during therapy, physicians should remain alert for signs of ulceration and bleeding, even in the absence of previous GI symptoms. Physicians should inform patients about the signs and symptoms of GI side effects and what steps to take if they occur.

Peptic Ulcer Disease: Patients with a history of active peptic ulcer disease should avoid using aspirin, which can cause gastric mucosal irritation and bleeding.

Precautions

General

Renal Failure: Avoid aspirin in patients with severe renal failure (glomerular filtration rate less than 10 mL/minute).

Hepatic Insufficiency: Avoid aspirin in patients with severe hepatic insufficiency.

Sodium Restricted Diets: Patients with sodium-retaining states, such as congestive heart failure or renal failure, should avoid sodium-containing buffered aspirin preparations because of their high sodium content.

Laboratory Tests: Aspirin has been associated with elevated hepatic enzymes, blood urea nitrogen and serum creatinine, hyperkalemia, proteinuria, and prolonged bleeding time.

Drug Interactions

Angiotensin Converting Enzyme (ACE) Inhibitors: The hyponatremic and hypotensive effects of ACE inhibitors may be diminished by the concomitant administration of aspirin due to its indirect effect on the renin-angiotensin conversion pathway.

Acetazolamide: Concurrent use of aspirin and acetazolamide can lead to high serum concentrations of acetazolamide (and toxicity) due to competition at the renal tubule for secretion.

Anticoagulant Therapy (Heparin and Warfarin): Patients on anticoagulation therapy are at increased risk for bleeding because of drug-drug interactions and the effect on platelets. Aspirin can displace warfarin from protein binding sites, leading to prolongation of both the prothrombin time and the bleeding time. Aspirin can increase the anticoagulant activity of heparin, increasing bleeding risk.

Anticonvulsants: Salicylate can displace protein-bound phenytoin and valproic acid, leading to a decrease in the total concentration of phenytoin and an increase in serum valproic acid levels.

Beta Blockers: The hypotensive effects of beta blockers may be diminished by the concomitant administration of aspirin due to inhibition of renal prostaglandins, leading to decreased renal blood flow, and salt and fluid retention.

Diuretics: The effectiveness of diuretics in patients with underlying renal or cardiovascular disease may be diminished by the concomitant administration of aspirin due to inhibition of renal prostaglandins, leading to decreased renal blood flow and salt and fluid retention.

Methotrexate: Salicylate can inhibit renal clearance of methotrexate, leading to bone marrow toxicity, especially in the elderly or renal impaired.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs): The concurrent use of aspirin with other NSAIDs should be avoided because this may increase bleeding or lead to decreased renal function.

Oral Hypoglycemics: Moderate doses of aspirin may increase the effectiveness of oral hypoglycemic drugs, leading to hypoglycemia.

Uricosuric Agents (Probenecid and Sulfinpyrazone): Salicylates antagonize the uricosuric action of uricosuric agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Administration of aspirin for 68 weeks at 0.5 percent in the feed of rats was not carcinogenic. In the Ames Salmonella assay, aspirin was not mutagenic; however, aspirin did induce chromosome aberrations in cultured human fibroblasts. Aspirin inhibits ovulation in rats. (See *Pregnancy*.)

Pregnancy: Pregnant women should only take aspirin if clearly needed. Because of the known effects of NSAIDs on the fetal cardiovascular system (closure of the ductus arteriosus), use during the third trimester of pregnancy should be avoided. Salicylate products have also been associated with alterations in maternal and neonatal hemostasis mechanisms, decreased birth weight, and with perinatal mortality.

Labor and Delivery: Aspirin should be avoided 1 week prior to and during labor and delivery because it can result in excessive blood loss at delivery. Prolonged gestation and prolonged labor due to prostaglandin inhibition have been reported.

Nursing Mothers: Nursing mothers should avoid using aspirin because salicylate is excreted in breast milk. Use of high doses may lead to rashes, platelet abnormalities, and bleeding in nursing infants.

Pediatric Use: Pediatric dosing recommendations for juvenile rheumatoid arthritis are based on well-controlled clinical studies. An initial dose of 90–130 mg/kg/day in divided doses, with an increase as needed for anti-inflammatory efficacy (target plasma salicylate levels of 150–300 mg/mL) are effective. At high doses (i.e., plasma levels of greater than 200 mg/mL), the incidence of toxicity increases.

Adverse Reactions

Many adverse reactions due to aspirin ingestion are dose-related. The following is a list of adverse reactions that have been reported in the literature. (See **Warnings.**)

Body as a Whole: Fever, hypothermia, thirst.

Cardiovascular: Dysrhythmias, hypotension, tachycardia.

Central Nervous System: Agitation, cerebral edema, coma, confusion, dizziness, headache, subdural or intracranial hemorrhage, lethargy, seizures.

Fluid and Electrolyte: Dehydration, hyperkalemia, metabolic acidosis, respiratory alkalosis.

Gastrointestinal: Dyspepsia, GI bleeding, ulceration and perforation, nausea, vomiting, transient elevations of hepatic enzymes, hepatitis, Reye's Syndrome, pancreatitis.

Hematologic: Prolongation of the prothrombin time, disseminated intravascular coagulation, coagulopathy, thrombocytopenia.

Hypersensitivity: Acute anaphylaxis, angioedema, asthma, bronchospasm, laryngeal edema, urticaria.

Musculoskeletal: Rhabdomyolysis.

Metabolism: Hypoglycemia (in children), hyperglycemia.

Reproductive: Prolonged pregnancy and labor, stillbirths, lower birth weight infants, antepartum and postpartum bleeding.

Respiratory: Hyperpnea, pulmonary edema, tachypnea.

Special Senses: Hearing loss, tinnitus. Patients with high frequency hearing loss may have difficulty perceiving tinnitus. In these patients, tinnitus cannot be used as a clinical indicator of salicylism.

Urogenital: Interstitial nephritis, papillary necrosis, proteinuria, renal insufficiency and failure.

Overdosage

Salicylate toxicity may result from acute ingestion (overdose) or chronic intoxication. The early signs of salicylic overdose (salicylism), including tinnitus (ringing in the ears),

occur at plasma concentrations approaching 200 mg/mL. Plasma concentrations of aspirin above 300 mg/mL are clearly toxic. Severe toxic effects are associated with levels above 400 mg/mL. (See **Clinical Pharmacology**.) A single lethal dose of aspirin in adults is not known with certainty but death may be expected at 30 g. For real or suspected overdose, a Poison Control Center should be contacted immediately. Careful medical management is essential.

Signs and Symptoms: In acute overdose, severe acid-base and electrolyte disturbances may occur and are complicated by hyperthermia and dehydration. Respiratory alkalosis occurs early while hyperventilation is present, but is quickly followed by metabolic acidosis.

Treatment: Treatment consists primarily of supporting vital functions, increasing salicylate elimination, and correcting the acid base disturbance. Gastric emptying and/ or lavage is recommended as soon as possible after ingestion, even if the patient has vomited spontaneously. After lavage and/or emesis, administration of activated charcoal, as a slurry, is beneficial, if less than 3 hours have passed since ingestion. Charcoal adsorption should not be employed prior to emesis and lavage. Severity of aspirin intoxication is determined by measuring the blood salicylate level. Acid-base status should be closely followed with serial blood gas and serum pH measurements. Fluid and electrolyte balance should also be maintained. In severe cases, hyperthermia and hypovolemia are the major immediate threats to life. Children should be sponged with tepid water. Replacement fluid should be administered intravenously and augmented with correction of acidosis. Plasma electrolytes and pH should be monitored to promote alkaline diuresis of salicylate if renal function is normal. Infusion of glucose may be required to control hypoglycemia. Hemodialysis and peritoneal dialysis can be performed to reduce the body drug content. In patients with renal insufficiency or in cases of life-threatening intoxication, dialysis is usually required. Exchange transfusion may be indicated in infants and young children.

8.2.2 Bayer Combination Product Labeling

8.2.2.1 Alka-Seltzer Plus®

Active Ingredients

Combination Ingredients (Per Tablet)	Cold	Cold Liqui-Gels	Flu Liqui-Gels	Cold and Sinus Effervescent	Cold and Sinus Liqui-Gels	Night Time Cold Liqui-Gels	Cold and Cough Liqui-Gels
Acetaminophen	250 mg	325 mg	325 mg	250 mg	325 mg	325 mg	325 mg
Chlorpheniramine maleate	2 mg	2 mg					2 mg
Phenylephrine hydrochloride	5 mg			5 mg			
Pseudoephedrine hydrochloride		30 mg	30 mg		30 mg	30 mg	30 mg
Dextromethorphan hydrobromide			10 mg			10 mg	10 mg
Doxylamine succinate						3.25 mg	

Inactive Ingredients (Liqui-Gels)

FD&C blue #1, FD&C red #40, Gelatin, Glycerin, Polyethylene Glycol, Polyvinyl Acetate Phthalate, Potassium Acetate, Povidone, Propylene Glycol, Sorbitol, Titanium Dioxide, Water

Inactive Ingredients (Tablets)

Acesulfame Potassium, Aspartame, Citric Acid, Flavors, Magnesium Stearate, Maltodextrin, Sodium Bicarbonate, Sorbitol

Indications

For temporary relief of these symptoms of colds and flu, runny nose, nasal and sinus congestion, headache, body aches and pains, sneezing, fever, or sore throat

Directions (Liqui-Gels)

Do not take more than the recommended dose (see Overdose Warning)

Adults and children 12 years and over: take 2 softgels with water every 4 hours, do not exceed 8 softgels in 24 hours or as directed by a doctor

Children 6 to under 12 years: take 1 softgel with water every 4 hours, do not exceed 4 softgels in 24 hours or as directed by a doctor

Children under 6 years: consult a doctor

Directions (Tablets)

Adults and children 12 years and over: take 2 tablets fully dissolved in 4 oz of water every 4 hours; do not exceed 8 tablets in 24 hours or as directed by a doctor

Children under 12 years: consult a doctor

Warnings

Alka-Seltzer Plus Liqui-Gels Cold Medicine

Sore throat warning: If sore throat is severe, persists for more than 2 days, is accompanied or followed by fever, headache, rash, nausea, or vomiting, consult a doctor promptly.

Do not use with any other products containing acetaminophen, if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric, or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product.

Ask a doctor before use if you have heart disease, high blood pressure, diabetes, thyroid disease, glaucoma; difficulty in urination due to enlargement of the prostate gland; or a breathing problem such as emphysema or chronic bronchitis

Ask a doctor or pharmacist before use if you are taking sedatives or tranquilizers.

When using this product, do not exceed recommended dosage. You may get drowsy. Avoid alcoholic drinks. Alcohol, sedatives, and tranquilizers may increase drowsiness. Be careful when driving a motor vehicle or operating machinery. Excitability may occur, especially in children.

Stop use and ask a doctor if nervousness, dizziness, or sleeplessness occurs; symptoms do not improve within 7 days (adults) or 5 days (children) or are accompanied by a fever; fever gets worse or lasts for more than 3 days; redness or swelling is present; or if new symptoms occur

If pregnant or breast-feeding, ask a health professional before use.

Keep out of reach of children.

Alka-Seltzer Plus Cold Medicine - Original

Sore throat warning: If sore throat is severe, persists for more than 2 days, is accompanied or followed by fever, headache, rash, nausea, or vomiting, consult a doctor promptly.

Do not use with any other products containing acetaminophen, if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric, or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product.

Ask a doctor before use if you have heart disease, high blood pressure, diabetes, thyroid disease, glaucoma, difficulty in urination due to enlargement of the prostate gland, or a breathing problem such as emphysema or chronic bronchitis

Ask a doctor or pharmacist before use if you are taking sedatives or tranquilizers, or are on a sodium-restricted diet

When using this product, do not exceed recommended dosage. Excitability may occur, especially in children. You may get drowsy. Avoid alcoholic drinks. Alcohol, sedatives, and tranquilizers may increase drowsiness. Be careful when driving a motor vehicle or operating machinery.

Stop use and ask a doctor if symptoms do not improve within 7 days or are accompanied by fever; new symptoms occur; fever gets worse or lasts for more than 3 days; redness or swelling is present or nervousness, dizziness, or sleeplessness occurs.

If pregnant or breast-feeding, ask a health professional before use.

Keep out of reach of children.

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.

Overdose Warning

Taking more than the recommended dose can cause serious health problems. In 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.

8.2.2.2 *Midol®*

Active Ingredients

Ingredient	Maximum Strength Midol® Teen	Maximum Strength Midol Menstrual	Maximum Strength Midol PMS
Acetaminophen	500 mg	500mg	500 mg
Pamabrom	25 mg		25 mg
Pyrilamine Maleate		15mg	15 mg
Caffeine		60mg	

Inactive Ingredients (Caplets)

Maximum Strength Midol® Teen	Maximum Strength Midol Menstrual	Maximum Strength Midol PMS
Carnauba Wax, Croscarmellose Sodium, D&C Red #7 Calcium Lake, FD&C Blue #2 Aluminum Lake, Hypromellose, Magnesium Stearate, Microcrystalline Cellulose, Propylene Glycol, Shellac, Starch, Titanium Dioxide, Triacetin	Carnauba Wax, Croscarmellose Sodium, FD&C Blue #2 Aluminum Lake, Hypromellose, Magnesium Stearate, Microcrystalline Cellulose, Propylene Glycol, Shellac, Starch, Titanium Dioxide, Triacetin	Carnauba Wax, Croscarmellose Sodium, D&C Red #30 Aluminum Lake, D&C Yellow #10 Aluminum Lake, Hydroxypropyl Hypromellose, Magnesium Stearate, Microcrystalline Cellulose, Propylene Glycol, Shellac, Starch, Titanium Dioxide, Triacetin

Inactive Ingredients (Gelcaps)

Maximum Strength Midol® Teen	Maximum Strength Midol Menstrual	Maximum Strength Midol PMS
N/A	Carnauba Wax, Croscarmellose Sodium, D&C Red #33 Lake, Disodium EDTA, FD&C Blue #1 Lake, Gelatin, Glycerin, Hydroxypropyl Hypromellose, Iron Oxide, Lecithin, Magnesium Stearate, Microcrystalline	Carnauba Wax, Croscarmellose Sodium, D&C Red #27 Aluminum Lake, Disodium EDTA, FD&C Blue #1, FD&C Red #40 Aluminum Lake, Gelatin, Glycerin, Hydroxypropyl Hypromellose, Iron Oxide,

Maximum Strength Midol® Teen	Maximum Strength Midol Menstrual	Maximum Strength Midol PMS
	Cellulose, Pharmaceutical Glaze, Simethicone, Starch, Stearic Acid, Titanium Dioxide, Triacetin	Lecithin, Magnesium Stearate, Microcrystalline Cellulose, Pharmaceutical Glaze, Simethicone, Starch, Stearic Acid, Titanium Dioxide, Triacetin

Indications

Indication	Maximum Strength Midol® Teen	Maximum Strength Midol Menstrual	Maximum Strength Midol PMS
Backaches	X	X	X
Bloating	X	X	X
Cramps	X	X	X
Fatigue		X	
Headaches	X	X	X
Muscular Aches	X	X	
Water-Weight Gain	X	X	X
Breast Tenderness		X	X

Directions

Do not take more than the recommended dose (see Overdose Warning)

Adults and children 12 years and over: Take 2 caplets (or gelcaps) with water. Repeat every 6 hours, as needed. Do not exceed 8 caplets (or gelcaps) per day. Under age 12: Consult your doctor

Warnings

Maximum Strength Midol® Teen

Do not use with any other product containing acetaminophen.

Stop use and ask a doctor if new symptoms occur; redness or swelling is present; or pain gets worse or lasts for more than 10 days

If pregnant or breast-feeding, ask a health professional before use.

Keep out of reach of children.

Maximum Strength Midol Menstrual

Do not use with any other product containing acetaminophen.

Ask a doctor before use if you have glaucoma, difficulty in urination due to enlargement of the prostate gland, or a breathing problem such as emphysema or chronic bronchitis

Ask a doctor or pharmacist before use if you are taking sedatives or tranquilizers.

When using this product, you may get drowsy. Avoid alcoholic drinks. Excitability may occur, especially in children. Alcohol, sedatives, and tranquilizers may increase drowsiness. Be careful when driving a motor vehicle or operating machinery. Limit the use of caffeine-containing medications, foods, or beverages because too much caffeine may cause nervousness, irritability, sleeplessness, and, occasionally, rapid heart beat. The recommended dose of this product contains about as much caffeine as a cup of coffee.

Stop use and ask a doctor if new symptoms occur, redness or swelling is present, pain gets worse or lasts for more than 10 days.

If pregnant or breast-feeding, ask a health professional before use.

Keep out of reach of children.

Maximum Strength Midol PMS

Do not use with any other product containing acetaminophen.

Ask a doctor before us if you have glaucoma, difficulty in urination due to enlargement of the prostate gland, a breathing problem such as emphysema or chronic bronchitis

Ask a doctor or pharmacist before use if you are taking sedatives or tranquilizers.

When using this product you may get drowsy. Excitability may occur, especially in children. Alcohol, sedatives, and tranquilizers may increase drowsiness. Avoid alcoholic drinks. Be careful when driving a motor vehicle or operating machinery

Stop use and ask a doctor if new symptoms occur, redness or swelling is present, pain gets worse or lasts for more than 10 days.

If pregnant or breast-feeding, ask a health professional before use.

Keep out of reach of children.

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.

Overdose Warning

Taking more than the recommended dose can cause serious health problems. In 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.

8.2.2.3 Vanquish®

Active Ingredients

194 mg Acetaminophen, 227 mg Aspirin and 33 mg Caffeine per caplet

Inactive Ingredients:

Aluminum Hydroxide, Colloidal Silicon Dioxide, Hypromellose, Magnesium Hydroxide, Microcrystalline Cellulose, Propylene Glycol, Starch, Titanium Dioxide, Zinc Stearate

Indications

Fast, safe, temporary relief of minor aches and pains associated with headaches, colds and flu, backaches, muscle aches, menstrual cramps and arthritis.

Directions

Do not take more than the recommended dose (see Overdose Warning)

Adults (12 years and over):Take 2 caplets with water every 6 hours, not to exceed 8 caplets in 24 hours unless directed by a doctor.

Children under 12 years: Consult a doctor.

Warnings

Reye's syndrome: Children and teenagers should not use this medicine for chicken pox or flu symptoms before a doctor is consulted about Reye's syndrome, a rare but serious illness reported to be associated with aspirin.

Do not use if you have had an allergic reaction to any pain reliever/fever reducer, with any other product containing acetaminophen.

Ask a doctor before use if you have, stomach problems (such as heartburn, upset stomach or stomach pain) that last or come back, bleeding problems, ulcers or asthma

Stop use and ask a doctor if: an allergic reaction occurs. Seek medical help right away; pain gets worse or lasts for more than 10 days; redness or swelling is present; new symptoms occur; ringing in the ears or loss of hearing occurs

If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use aspirin during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.

Keep out of reach of children.

Overdose Warning

Taking more than the recommended dose can cause serious health problems. In 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.

Alcohol Warning

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

Drug Interaction Precaution

Ask a doctor or pharmacist before use if you are taking a prescription drug for anticoagulation (blood thinning), gout, diabetes, or arthritis.

8.2.3 Acetaminophen (Tylenol® Regular Strength- McNeil) Product Labeling

Active Ingredients

325 mg acetaminophen

Inactive Ingredients

Cellulose, corn starch, magnesium stearate, sodium starch glycolate

Indications

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

Directions

Do not take more than directed.

Adults and Children 12 years of Age and Older: Take 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.

Children 6-11 years of age. Take 1 tablet every 4 to 6 hours as needed. Do not take more than 5 tablets in 24 hours.

Children under 6 years of age: Do not use these adult Regular Strength product in children under 6 years of age. This will provide more than the recommended dose (overdose) of TYLENOL® and could cause serious health problems.

Warnings

Do Not Use:

- With any other product containing acetaminophen
- For more than 10 days for pain unless directed by a doctor.
- For more than 3 days for fever unless directed by a doctor.

Stop Using and Ask a Doctor If:

- Symptoms do not improve
- New symptoms occur
- Pain or fever persists or gets worse
- Redness or swelling is present

If you are pregnant or breast-feeding, ask a health professional before use.

Keep out of the reach of children. In 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.

Alcohol Warnings

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.

Overdosage Information for Professionals

Acetaminophen in massive overdosage may cause hepatic toxicity in some patients. In adults and adolescents (>/=12 years of age), hepatic toxicity may occur following ingestion of greater than 7.5 to 10 grams over a period of 8 hours or less. Fatalities are infrequent (less than 3-4% of untreated cases) and have rarely been reported with overdoses of less than 15 grams. In children (<12 years of age), an acute overdosage of less than 150 mg/kg has not been associated with hepatic toxicity. Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis, and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion. In adults and adolescents, any individual presenting with an unknown amount of acetaminophen ingested or with a questionable or unreliable history about the time of ingestion should have a plasma acetaminophen level drawn and be treated with N -acetylcysteine. For full prescribing information, refer to the N-acetylcysteine package insert. Do not await results of assays for plasma acetaminophen levels before initiating treatment with N -acetylcysteine. The following additional procedures are recommended: Promptly initiate gastric decontamination of the stomach. A plasma acetaminophen assay should be obtained as early as possible, but no sooner than four hours following ingestion. If an acetaminophen extended release product is involved, it may be appropriate to obtain an additional plasma acetaminophen level 4-6 hours following the initial acetaminophen level. If either acetaminophen level plots above the treatment line on the acetaminophen overdose nomogram, N -acetylcysteine treatment should be continued for a full course of therapy. Liver function studies should be obtained initially and repeated at 24-hour intervals.

Serious toxicity or fatalities have been extremely infrequent following an acute acetaminophen overdose in young children, possibly because of differences in the way they metabolize acetaminophen. In children, the maximum potential amount ingested can be more easily estimated. If more than 150 mg/kg or an unknown amount was ingested, obtain a plasma acetaminophen level as soon as possible, but no sooner than 4 hours following ingestion. If an acetaminophen extended release product is involved, it may be appropriate to obtain an additional plasma acetaminophen level 4-6 hours following the initial acetaminophen level. If either acetaminophen level plots above the treatment line on the acetaminophen overdose nomogram, N -acetylcysteine treatment

should be initiated and continued for a full course of therapy. If an assay cannot be obtained and the estimated acetaminophen ingestion exceeds 150 mg/kg, dosing with N - acetylcysteine should be initiated and continued for a full course of therapy.

For additional emergency information, call your regional poison center or call the Rocky Mountain Poison Center toll-free, (1-800-525-6115).

Alcohol Information for Professionals

Chronic heavy alcohol abusers may be at increased risk of liver toxicity from excessive acetaminophen use, although reports of this event are rare. Reports usually involve cases of severe chronic alcoholics and the dosages of acetaminophen most often exceed recommended doses and often involve substantial overdose. Healthcare professionals should alert their patients who regularly consume large amounts of alcohol not to exceed recommended doses of acetaminophen.

8.3 Labeling Recommendations

To ensure safe product use, Bayer makes the following recommendations for OTC analgesic product labeling:

8.3.1 Products Containing Aspirin

Bayer does not recommend any further warnings for aspirin products, as the current Drug Facts Label adequately highlights safe dosing and self-medication regimens, including contraindications for use in certain populations.

Bayer

Original Strength BAYER Aspirin Caplets

Drug Facts

Active ingredient (in each caplet) — **Purposes**

Aspirin 325 mg ..... Pain reliever/fever reducer

Uses temporarily relieves

- headache
- muscle pain
- toothache
- menstrual pain
- pain and fever of colds
- minor pain of arthritis

Warnings

Reye's syndrome: Children and teenagers should not use this medicine for chicken pox or flu symptoms before a doctor is consulted about Reye's syndrome, a rare but serious illness reported to be associated with aspirin.

Alcohol warning: If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take aspirin or other pain relievers/fever reducers. Aspirin may cause stomach bleeding.

Do not use if you are allergic to aspirin or any other pain reliever/fever reducer

Ask a doctor before use if you have

- stomach problems (such as heartburn, upset stomach, or stomach pain) that continue or come back
- bleeding problems
- ulcers
- asthma

Ask a doctor or pharmacist before use if you are taking a prescription drug for

- anticoagulation (blood thinning)
- gout
- diabetes
- arthritis

Stop use and ask a doctor if

- an allergic reaction occurs. Seek medical help right away.
- pain gets worse or lasts for more than 10 days
- redness or swelling is present
- fever lasts for more than 3 days
- new symptoms occur
- ringing in the ears or loss of hearing occurs

If pregnant or breast-feeding, ask a health professional before use. **It is especially important not to use aspirin during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.**

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- drink a full glass of water with each dose
- adults and children 12 years and over: take 1 or 2 caplets every 4 hours not to exceed 12 caplets in 24 hours
- children under 12 years: consult a doctor

Other information

- save carton for full directions and warnings
- store at room temperature

Inactive ingredients cellulose, hypromellose, starch, triacetin

Questions or comments? 1-800-331-4536 or www.bayeraspirin.com

8.3.2 Products Containing Acetaminophen

For all products containing acetaminophen, Bayer recommends the adoption of the suggested labeling by the Consumer Health Care Products Association (CHPA), as noted in Table 11.

Table 11: Consumer Healthcare Products Association Suggested Labeling

Label	Suggested Language
Principal Display Panel:	The Principal Display Panel (PDP) is to declare the active ingredients of single ingredient and multi-symptom relief (i.e., combination) acetaminophen-containing products in a readable type size and type face. [Note: this is already a requirement for single ingredient OTC drug products.]
Drug Facts Label:	Active Ingredient Section: This program includes color highlighting of acetaminophen in the active ingredient section, which is the first listed information on the "back" of the OTC package under "Drugs Facts."
Cross-dosing:	Within Drug Facts Label Warnings Section: "Do not use with other acetaminophen containing products," or "Do not use with any medicines containing acetaminophen," or equivalent wording
Overdose Warning:	Within the Drug Facts Warnings Section: "Overdose Warning: Taking more than the recommended dose can cause serious health problems. In 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."
Overdose Warning:	Within Drug Facts Directions Section: A statement under Directions is to caution to use recommended dosages and to reference the overdose warning in the Warnings section of the Drug Facts box, as follows: "Do not use more than directed - (see overdose warning)," or "take only as recommended - (see overdose warning)," or equivalent wording.
Flag the Label	The flag-the-label component of the voluntary acetaminophen program will be carried for at least 12 months.
Implementation Dates	Implementation dates for the voluntary acetaminophen labeling program will be at the next label printing or as follows: *For: OTC monograph acetaminophen-containing OTC drug products:* 70% of SKU's or volume manufactured after December 31, 2002 will be in voluntary compliance; 30% (the remainder) of SKU's or volume manufactured after June 30, 2003 will be in voluntary compliance. *For: NDA'd acetaminophen-containing OTC drug products:*

Label	Suggested Language
	By August 31, 2002, submission of labeling of products not requiring significant packaging changes; By December 31, 2002, submission of labeling of products requiring significant packaging changes.

As can be seen in the Drug Facts Label of each Bayer product containing acetaminophen, shown below, Bayer supports implementation of the CHPA labeling to ensure safe use of acetaminophen-containing products. The only deviation to the CHPA labeling that Bayer, along with many other industry members, has made is with regard to highlighting. Bayer has opted to highlight all active ingredients on the Drug Facts Label, rather than just acetaminophen, as suggested in the CHPA labeling.

Bayer

Alka-Seltzer Plus Cold Medicine - Original

Drug Facts

Active ingredients (in each tablet) — Purposes

Acetaminophen 250 mg	Pain reliever/fever reducer
Chlorpheniramine maleate 2 mg	Antihistamine
Phenylephrine HCl 5 mg	Nasal decongestant

Uses

provides temporary relief of these symptoms

- runny nose
- nasal and sinus congestion
- headache
- body aches and pains
- sneezing
- fever
- sore throat

Warnings

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.

Sore throat warning: If sore throat is severe, persists for more than 2 days, is accompanied or followed by fever, headache, rash, nausea, or vomiting, consult a doctor promptly.

Do not use

- with any other products containing acetaminophen
- if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric, or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product.

Ask a doctor before use if you have

- heart disease
- high blood pressure
- diabetes
- thyroid disease
- glaucoma
- difficulty in urination due to enlargement of the prostate gland
- a breathing problem such as emphysema or chronic bronchitis

Ask a doctor or pharmacist before use if you are

- taking sedatives or tranquilizers
- on a sodium-restricted diet

When using this product

- **do not exceed recommended dosage**
- excitability may occur, especially in children
- you may get drowsy
- avoid alcoholic drinks
- alcohol, sedatives, and tranquilizers may increase drowsiness
- be careful when driving a motor vehicle or operating machinery

Stop use and ask a doctor if

- symptoms do not improve within 7 days or are accompanied by fever
- new symptoms occur
- fever gets worse or lasts for more than 3 days
- redness or swelling is present
- nervousness, dizziness, or sleeplessness occurs

If pregnant or breast-feeding, ask a health professional before use.

Keep out of reach of children.

Overdose Warning: Taking more than the recommended dose can cause serious health problems. In 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.

Directions

- do not take more than the recommended dose (see **Overdose Warning**)

adults and children 12 years and over	take 2 tablets fully dissolved in 4 oz of water every 4 hours	do not exceed 8 tablets in 24 hours or as directed by a doctor
children under 12 years	consult a doctor	

Other information

- **each tablet contains:** sodium 476 mg
- **phenylketonurics:** contains phenylalanine 8.4 mg per tablet
- this product does not contain phenylpropanolamine (PPA)
- protect from excessive heat

Inactive ingredients

acesulfame potassium, aspartame, citric acid, flavors, magnesium stearate, maltodextrin, sodium bicarbonate, sorbitol

Questions or comments?

1-800-800-4793 or www.alka-seltzerplus.com

Bayer

Alka-Seltzer Plus Liqui-Gels Cold Medicine

Drug Facts

Active ingredients (in each softgel) — Purposes

Acetaminophen 325 mg	Pain reliever/fever reducer
Chlorpheniramine maleate 2 mg	Antihistamine
Pseudoephedrine HCl 30 mg	Nasal decongestant

Uses

provides temporary relief of these symptoms of colds and flu:

- runny nose
- nasal and sinus congestion
- headache
- body aches and pains
- sneezing
- fever
- sore throat

Warnings

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.
Sore throat warning: If sore throat is severe, persists for more than 2 days, is accompanied or followed by fever, headache, rash, nausea, or vomiting, consult a doctor promptly.

Do not use

- with any other products containing acetaminophen
- if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric, or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product

Ask a doctor before use if you have

- heart disease
- high blood pressure
- diabetes
- thyroid disease
- glaucoma
- difficulty in urination due to enlargement of the prostate gland
- a breathing problem such as emphysema or chronic bronchitis

Ask a doctor or pharmacist before use if you are taking sedatives or tranquilizers

When using this product

- **do not exceed recommended dosage**
- you may get drowsy
- avoid alcoholic drinks
- alcohol, sedatives, and tranquilizers may increase drowsiness
- be careful when driving a motor vehicle or operating machinery
- excitability may occur, especially in children

Stop use and ask a doctor if

- nervousness, dizziness, or sleeplessness occurs
- symptoms do not improve within 7 days (adults) or 5 days (children) or are accompanied by a fever
- fever gets worse or lasts for more than 3 days
- redness or swelling is present
- new symptoms occur

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children.
Overdose Warning: Taking more than the recommended dose can cause serious health problems. In 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.

Directions

- do not take more than the recommended dose (see **Overdose Warning**)

adults and children 12 years and over	take 2 softgels with water every 4 hours	do not exceed 8 softgels in 24 hours or as directed by a doctor
children 6 to under 12 years	take 1 softgel with water every 4 hours	do not exceed 4 softgels in 24 hours or as directed by a doctor
children under 6 years	consult a doctor	

Other information

- this product does not contain phenylpropanolamine (PPA)
- store at room temperature and avoid excessive heat

Inactive ingredients

FD&C blue #1, FD&C red #40, gelatin, glycerin, polyethylene glycol, polyvinyl acetate phthalate, potassium acetate, povidone, propylene glycol, sorbitol, titanium dioxide, water

Questions or comments?

1-800-800-4793 or www.alka-seltzerplus.com

Bayer

Maximum Strength Midol Menstrual – Caplets

Drug Facts

Active ingredients (in each caplet) — **Purpose**

Acetaminophen 500 mg ..... Pain reliever
Caffeine 60 mg ..... Stimulant
Pyrilamine maleate 15 mg ..... Diuretic

Uses for the temporary relief of these symptoms associated with menstrual periods:

- cramps
- bloating
- water-weight gain
- breast tenderness
- headache
- backache
- muscle aches
- fatigue

Warnings

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.

Do not use with any other product containing acetaminophen.

Ask a doctor before use if you have

- glaucoma
- difficulty in urination due to enlargement of the prostate gland
- a breathing problem such as emphysema or chronic bronchitis

Ask a doctor or pharmacist before use if you are taking sedatives or tranquilizers.

When using this product

- you may get drowsy
- avoid alcoholic drinks
- excitability may occur, especially in children
- alcohol, sedatives, and tranquilizers may increase drowsiness
- be careful when driving a motor vehicle or operating machinery
- limit the use of caffeine-containing medications, foods, or beverages because too much caffeine may cause nervousness, irritability, sleeplessness, and, occasionally, rapid heart beat. The recommended dose of this product contains about as much caffeine as a cup of coffee.

Stop use and ask a doctor if

- new symptoms occur
- redness or swelling is present
- pain gets worse or lasts for more than 10 days

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children.
Overdose Warning: Taking more than the recommended dose can cause serious health problems. In 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.

Directions

- do not take more than the recommended dose (see **Overdose Warning**)
- adults and children 12 years and older
  - take 2 caplets with water
  - repeat every 6 hours, as needed
  - do not exceed 8 caplets per day
- children under 12 years, consult a doctor

Other information

- store at room temperature

Inactive ingredients carnauba wax, croscarmellose sodium, FD&C blue #2 aluminum lake, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, propylene glycol, shellac, starch, titanium dioxide, triacetin

Questions or comments? 1-800-331-4536 or www.midol.com

Bayer

Maximum Strength Midol
PMS Symptom Relief Formula - Caplets

Drug Facts

Active ingredients (in each caplet)	Purpose
Acetaminophen 500 mg	Pain reliever
Pamabrom 25 mg	Diuretic
Pyrilamine maleate 15 mg	Diuretic

Uses for the temporary relief of these symptoms associated with menstrual periods
- bloating
- water-weight gain
- cramps
- breast tenderness
- headache
- backache

Warnings

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.

Do not use with any other product containing acetaminophen.

Ask a doctor before use if you have
- glaucoma
- difficulty in urination due to enlargement of the prostate gland
- a breathing problem such as emphysema or chronic bronchitis

Ask a doctor or pharmacist before use if you are taking sedatives or tranquilizers.

When using this product
- you may get drowsy
- excitability may occur, especially in children
- alcohol, sedatives, and tranquilizers may increase drowsiness
- avoid alcoholic drinks
- be careful when driving a motor vehicle or operating machinery

Stop use and ask a doctor if
- new symptoms occur
- redness or swelling is present
- pain gets worse or lasts for more than 10 days

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children.
Overdose Warning: Taking more than the recommended dose can cause serious health problems. In 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.

Directions
- do not take more than the recommended dose (see **Overdose Warning**)
- adults and children 12 years and older
  - take 2 caplets with water
  - repeat every 6 hours, as needed
  - do not exceed 8 caplets per day
- children under 12 years, consult a doctor

Other information - store at room temperature

Inactive ingredients carnauba wax, croscarmellose sodium, D&C red #30 aluminum lake, D&C yellow #10 aluminum lake, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, propylene glycol, shellac, starch, titanium dioxide, triacetin

Questions or comments? 1-800-331-4536 or www.midol.com

Bayer

Maximum Strength Midol Teen Formula - Caplets

Drug Facts

Active ingredients (in each caplet) — **Purpose**

Acetaminophen 500 mg ..... Pain reliever
Pamabrom 25 mg ..... Diuretic

Uses for the temporary relief of these symptoms associated with menstrual periods:

- cramps
- bloating
- water-weight gain
- headache
- backache
- muscle aches

Warnings

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.

Do not use with any other product containing acetaminophen.

Stop use and ask a doctor if

- new symptoms occur
- redness or swelling is present
- pain gets worse or lasts for more than 10 days

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children.
Overdose Warning: Taking more than the recommended dose can cause serious health problems. In 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.

Directions

- do not take more than the recommended dose (see **Overdose Warning**)
- adults and children 12 years and older
  - take 2 caplets with water
  - repeat every 6 hours, as needed
  - do not exceed 8 caplets per day
- children under 12 years, consult a doctor

Other information store at room temperature

Inactive ingredients carnauba wax, croscarmellose sodium, D&C red #7 calcium lake, FD&C blue #2 aluminum lake, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, propylene glycol, shellac, starch, titanium dioxide, triacetin

Questions or comments? 1-800-331-4536 or www.midol.com

Bayer

Vanquish Extra-Strength Pain Reliever

Drug Facts

Active ingredients *(in each caplet)* — **Purpose**

Acetaminophen 194 mg ..... Pain reliever
Aspirin 227 mg ..... Pain reliever
Caffeine 33 mg ..... Pain reliever aid

Uses temporarily relieves minor pain due to

- headache
- backache
- menstrual cramps
- arthritis
- colds and flu
- muscle aches

Warnings

Reye's syndrome: Children and teenagers should not use this medicine for chicken pox or flu symptoms before a doctor is consulted about Reye's syndrome, a rare but serious illness reported to be associated with aspirin.

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

Do not use

- if you have had an allergic reaction to any pain reliever/fever reducer
- with any other product containing acetaminophen

Ask a doctor before use if you have

- stomach problems (such as heartburn, upset stomach or stomach pain) that last or come back
- bleeding problems • ulcers • asthma

Ask a doctor or pharmacist before use if you are taking a prescription drug for

- anticoagulation (blood thinning)
- gout • diabetes • arthritis

Stop use and ask a doctor if

- an allergic reaction occurs. Seek medical help right away.
- pain gets worse or lasts for more than 10 days
- redness or swelling is present
- new symptoms occur
- ringing in the ears or loss of hearing occurs

If pregnant or breast-feeding, ask a health professional before use. **It is especially important not to use aspirin during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.**

Keep out of reach of children.

Overdose Warning: Taking more than the recommended dose can cause serious health problems. In 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.

Directions

- do not take more than the recommended dose (see **Overdose Warning**)
- adults and children 12 years and over: take 2 caplets with water every 6 hours, not to exceed 8 caplets in 24 hours unless directed by a doctor
- children under 12 years: consult a doctor

Other information

- save carton for full directions and warnings
- store at room temperature
- buffered with aluminum hydroxide and magnesium hydroxide

Inactive ingredients aluminum hydroxide, colloidal silicon dioxide, hypromellose, magnesium hydroxide, microcrystalline cellulose, propylene glycol, starch, titanium dioxide, zinc stearate

Questions or comments? 1-800-331-4536 or www.bayercare.com

8.3.3 Products Containing Ibuprofen

8.4 Efficacy Overview

Generally recognized as effective agents in the Internal Analgesic, Antipyretic and Antirheumatic Drug Products for Over-the-Counter Human Use; Tentative Final Monograph (TFM) (FDA, 1988), aspirin and acetaminophen are widely used ingredients for short-term treatment of mild to moderate pain and reduction of fever. As noted in the Final Rule for aspirin labeling, aspirin is also recognized as effective in reducing the risk of recurrent ischemic stroke and stroke after a transient ischemic attack (TIA), suspected acute myocardial infarction (MI), prevention of recurrent MI, unstable angina pectoris, chronic stable angina pectoris, and for use in some revascularization procedures in selected patients (FDA, 1998). Additionally, unlike acetaminophen, aspirin is indicated under professional labeling for relief of the signs and symptoms of rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, spondylarthropathies, and arthritis and pleurisy associated with systemic lupus erythematosus (SLE) (FDA, 1998).

As noted in the product labeling, it is clear that aspirin carries a broader range of therapeutic benefits than acetaminophen. Likewise, aspirin has been shown to be more effective than acetaminophen in specific conditions:

- Aspirin may be more effective than acetaminophen for relief of pain associated with inflammation (Lipman, 1996)
- Aspirin provides superior relief for dysmenorrhea as compared with acetaminophen (Lipman, 1996)
- Unlike acetaminophen, aspirin is approved for treatment of migraine (CDER, 2001)
- The anti-platelet and anti-inflammatory effects of aspirin are superior to that of acetaminophen, which has no effect (Lipman, 1996)

8.4.1 Mechanism of Action

The differing mechanisms of action of aspirin and acetaminophen account for the unique efficacy attributes of each ingredient. Table 12 summarizes the different mechanisms of action and consequent therapeutic effects of aspirin and acetaminophen.

Table 12: Efficacy Based on Mechanism of Action of Aspirin and Acetaminophen

	Aspirin		Acetaminophen
Mechanism	Primarily peripheral inhibition of prostaglandins	Inactivation of COX enzyme by irreversible acetylation	Mechanism unknown: may involve central nervous system inhibition of prostaglandins
Therapeutic Effect	Analgesia Antipyresis Antiinflammatory	Cardiovascular	Analgesia Antipyresis

The clinical efficacy of aspirin is based on its interaction with two isoforms of the cyclooxygenase (COX) enzyme, COX-1 and COX-2. This interaction ultimately inhibits prostaglandin synthesis from arachidonic acid. Prostaglandins are mediators of pain, and inflammation, and the inhibition of their synthesis provides analgesia and reduction in inflammation (Green, 2001). Likewise, the proven antipyretic effects of aspirin are the result of prostaglandin inhibition in the CNS, which affects temperature regulation. Prostaglandins and COX activity are associated with various biologic activities and body maintenance functions. The COX-1 enzyme, for example, is expressed in many tissues, including platelets, endothelium, gastric mucosa, renal tubules, and brain; and the COX-2 isoform, is an inducible enzyme responsible for inflammation caused by prostaglandin synthesis at the site of injury. Prostaglandins play a role in blood flow, thus offering benefits to the kidney and protection of the gastric mucosa from acid damage (Green, 2001).

One key mechanistic component of aspirin's therapeutic effects is its inhibition of the synthesis of thromboxane, which is involved with platelet aggregation. By inhibiting thromboxane synthesis, aspirin attenuates platelet aggregation (Green, 2001). Unlike similar compounds known as nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin irreversibly acetylates the COX-1 enzyme, thus preventing platelet thromboxane production and aggregation. The inhibition of platelet aggregation results in a unique benefit for aspirin in prevention of thromboembolic complications, including the risk for myocardial infarction and stroke (Green, 2001). While nucleated cells can regenerate enzymes and produce prostaglandins following exposure to aspirin, platelets do not have nuclei or ability to regenerate enzymes and thromboxane synthesis is inhibited for the life of the platelet. Some nucleated cells can also generate thromboxane through COX-2, however inhibition of COX-2 can occur at aspirin doses > 500 mg/day.

Like aspirin, acetaminophen possesses analgesic and antipyretic activity; however, its precise mechanism of action is unknown. It is suggested that acetaminophen exerts its analgesic effects through both peripheral and central mechanisms involving prostaglandin and nonprostaglandin pathways (Guzman, 1967; Ferriera, 1978; Tjolsen, 1991; Malmberg, 1992; Moore, 1992). The antipyretic effects of acetaminophen may be attributable to its inhibition of the COX enzyme in the CNS (Flower, 1972), as acetaminophen has almost equivalent potency to aspirin in blocking COX in the brain tissue (Ferriera, 1974; Brune, 1992). Acetaminophen, however, is nearly 10 times less potent than aspirin as a peripheral COX inhibitor; therefore it does not effectively inhibit prostaglandin production in peripheral tissues. Likewise, the anti-inflammatory activity of acetaminophen is considerably weaker than aspirin (Glenn, 1977; Desjardins, 1998).

8.4.2 Pharmacokinetics and Individual Variability

Because there is generally a positive relationship between plasma concentration of a drug and analgesic activity (Seymour, 1982; Laska, 1986), absorption rate and circulating drug concentration are important determinants of analgesic efficacy. It has been suggested that analgesic formulations with enhanced absorption rates may be more effective in treating acute pain, however, no single OTC analgesic ingredient has demonstrated superiority over competing ingredients with respect to onset of action, despite differences in apparent rates of absorption (Jamali, 1999).

Although all OTC analgesics are generally considered to be equivalent in therapeutic benefit for OTC indications, individuals seek the fastest-acting, longest-lasting treatment with the fewest side effects. There is a significant degree of individual variability in the pharmacokinetics of drug metabolism and perceived therapeutic effects. This influences consumer use patterns. A recent survey of consumer use demonstrates that two thirds of consumers feel that their OTC pain medication is not completely or not very effective, causing frequent ingredient switching (NFO Research, Inc., 1999).

Both the desired clinical effect (analgesic, antipyretic, anti-inflammatory, cardiovascular) and inter-individual differences play an important role in a drug's clinical efficacy. Because of individual responses to drug ingredients and dosing regimens, it is beneficial to provide consumers with latitude. Physicians recognize the unique differences between individuals leading to variability in clinical response, and individualize treatment regimens to seek optimal effectiveness in each individual. Likewise, the FDA recognizes the variations in individual responses to dosing regimens, as conclusions regarding the dosing of many drugs are established by looking at individual patient data rather than mean data to determine advantages in speed of onset, duration of action, or maximum effect. In fact, the FDA favors the evaluation of individual patient responses rather than mean data to establish effectiveness in its NDA review. For example, labels on ibuprofen, naproxen sodium and ketoprofen, three analgesic ingredients available OTC, direct patients to take one tablet/caplet, however, if the patient knows from previous experience that a one-tablet/caplet dose is not sufficient, he/she may take 2 tablets/caplets to gain the desired therapeutic relief.

Studies suggest that an individual's pain state could influence the analgesic response to an OTC analgesic. For example, in a retrospective analysis of plasma ibuprofen concentration curves, erratic absorption was noted in patients experiencing pain, while healthy volunteers showed relatively uniform absorption rates (Jamali, 1999). Further analyses of absorption suggest that doses that produce satisfactory serum analgesic concentrations in healthy subjects may not be efficacious in a patient with pain (Jamali, 1999). Such data support the importance of various dosing regimens for all analgesic products, including extra-strength formulations for more severe pain.

Aspirin has been shown to have significant therapeutic benefit; however, interindividual differences in the pharmacokinetics of aspirin and metabolic profiles (Rainsford, 1980; Seymour, 1986; Seymour, 1992) warrant the use of different dosing regimens in different patients. Preparations of 1000 mg aspirin may be required in some patients in order to achieve adequate pain relief. As previously noted, individual variability was recognized by the FDA in the proposed Monograph for OTC Internal Analgesic, Antipyretic and Antirheumatic Products (1977), where it is stated that the shape of the dose response curve above 650 mg dosages suggests that some individuals with some types of pain may obtain greater pain relief with single doses of 975-1300 mg.

8.4.3 Clinical Studies

While it is difficult to compare the effectiveness of various OTC agents in clinical trials, numerous studies have been conducted to evaluate the relative efficacy of OTC analgesics in dental post-surgical pain, sore throat pain, muscle strain, menstrual cramp pain, headaches, and fever reduction (Hersh, 2000a). The adult oral aspirin and acetaminophen dosage recommended by the FDA for relief of mild to moderate pain or fever reduction is 325-650 mg every 4 hours, or 325-500 mg every 3 hours, or 650-1000 mg every 6 hours while symptoms persist, not to exceed 4 g in 24 hours (FDA, 1988). Aspirin is additionally indicated under professional labeling for cardioprotection and treatment of inflammatory conditions at the dosing schedules outlined in Table 13 (FDA, 1998).

Table 13: Professional Dosing of Aspirin

Indication	Aspirin Dose
Ischemic Stroke and TIA	50-325 mg once a day. Continue therapy indefinitely.
Suspected Acute MI	The initial dose of 160-162.5 mg is administered as soon as an MI is suspected. The maintenance dose of 160-162.5 mg a day is continued for 30 days post-infarction. After 30 days, consider further therapy based on dosage and administration for prevention of recurrent MI.
Prevention of Recurrent MI	75-325 mg once a day. Continue therapy indefinitely.
Unstable Angina Pectoris	75-325 mg once a day. Continue therapy indefinitely.
Chronic Stable Angina Pectoris	75-325 mg once a day. Continue therapy indefinitely.
CABG	325 mg daily starting 6 hours post-procedure. Continue therapy for 1 year post-procedure.
PTCA	The initial dose of 325 mg should be given 2 hours pre-surgery. Maintenance dose is 160-325 mg daily. Continue therapy indefinitely.
Carotid Endarterectomy	Doses of 80 mg once daily to 650 mg twice daily, started pre surgery are recommended. Continue therapy indefinitely.
Rheumatoid Arthritis	The initial dose of 3 g a day in divided doses. Increase as needed for anti-inflammatory efficacy with target plasma salicylate levels of 150-300 µg/mL. At high doses (i.e., plasma levels greater than 200 mg/mL), the incidence of toxicity increases.

Indication	Aspirin Dose
Juvenile Rheumatoid Arthritis	Initial dose is 90-130 mg/kg/day in divided doses. Increase as needed for anti-inflammatory efficacy with target plasma salicylate levels of 150-300 μg/mL. At high doses (i.e., plasma levels greater than 200 mg/mL), the incidence of toxicity increases.
Spondyloarthropathies	Up to 4 g per day in divided doses.
Osteoarthritis	Up to 3 g per day in divided doses.
Arthritis and Pleurisy of SLE	The initial dose is 3 g a day in divided doses. Increase as needed for anti-inflammatory efficacy with target plasma salicylate levels of 150-300 μg/mL. At high doses (i.e., plasma levels greater than 200 mg/mL), the incidence of toxicity increases.

8.4.3.1 Analgesia

Pain relief is a subjective outcome influenced by a host of factors, including prior experience and a belief that the pain will be relieved. Because of the psychological aspects of pain, it is not surprising that medication regimens may exert varying degrees of benefits in different people. Despite individual variability, both aspirin and acetaminophen are effective agents and offer significant analgesic effects over placebo (Hersh, 2000b). Although generally classified as "mild analgesics," aspirin and acetaminophen are effective agents that offer analgesic benefits throughout a range of doses.

Under OTC dosing regimens, aspirin and acetaminophen are generally recognized as equally effective and associated with similar times to onset of analgesic effect. Studies have shown that 650 mg aspirin is equivalent to 650 mg acetaminophen in analgesic onset (within 60 minutes), peak effect, and duration of action (approximately 4 hours) (Cooper, 1983). Both ingredients have been clinically shown to have a dose-response relationship up to the OTC approved 1000 mg per dose, and data suggest that an increased benefit may continue in doses up to ≥ 1200 mg (Von Graffenreid, 1980; Cooper 1981, Seymour 1982; Cooper 1983, Edwards, 1999).

As noted, the efficacy of aspirin over placebo has been demonstrated through numerous clinical studies, and provides support for aspirin's full range of analgesic doses. A study on headache pain relief reports an increased benefit of 650 mg aspirin over lower aspirin doses, with the following percentages of patients experiencing headache pain relief: 81% at 650 mg; 68% at 325 mg; 57% at 163 mg; and 57% with placebo (Murray, 1964).

Additionally, two meta-analyses involving 7487 patients taking aspirin for various conditions suggest that the analgesic dose-response curve shows a positive slope between 650 mg and 1200-1300 mg, and demonstrates that 650 mg, while effective, is less effective than a maximum dose (Laska, 1982; Edwards, 1999).

A recent prospective, randomized double-blind single-dose study comparing 1000 mg aspirin and the most commonly prescribed dose of the leading acetaminophen-containing prescription pain reliever (Tylenol® with Codeine #3: 300 mg acetaminophen plus 30 mg codeine phosphate) in severe pain associated with tension-type headaches found the aspirin therapy to be as effective as the prescription strength Tylenol® with Codeine (MacEachern, 2001a). Similarly, a single-dose study of 1000 mg aspirin, Tylenol® with Codeine #3 (300 mg acetaminophen plus 30 mg codeine phosphate) and placebo in subjects with dental pain demonstrated that while all treatments were well tolerated, aspirin was significantly more effective than Tylenol® with Codeine at some time points (MacEachern, 2001b).

Like aspirin, acetaminophen has demonstrated efficacy over analgesic combinations including codeine (Cooper, 1980), a finding that is not surprising considering that the analgesic effects of aspirin and acetaminophen are generally recognized as equivalent on a milligram-to-milligram basis (Cooper, 1983). Some study data, however, suggest that aspirin may have greater analgesic efficacy than acetaminophen. A study of headache pain reports that 650 mg aspirin offers analgesic efficacy equal to or exceeding that of 1000 mg acetaminophen (Peters, 1983).

It should also be noted that while 1000 mg of aspirin may offer analgesic benefit over 650 mg in some individuals, (Laska, 1982; Edwards, 1999), a finding that is largely based on individual variation and pharmacokinetics, it is less clear if 1000 mg acetaminophen offers a significant analgesic benefit over 650 mg. While data suggest that the therapeutic effects of acetaminophen exhibits a dose-response curve (Cooper, 1981; Cooper 1983), it is unclear if the therapeutic benefits outweighs the potential risk for serious adverse events at the higher doses.

8.4.3.2 Antipyresis

Aspirin and acetaminophen are effective agents in reducing fever in children, and appear to be equivalent on a milligram-for-milligram basis (Yaffee, 1981). As antipyretics, aspirin and acetaminophen have equivalent rates of onset and peak effects (Tarlin, 1972).

8.4.3.3 Anti-inflammatory

Both aspirin and acetaminophen are indicated for the treatment of minor pain associated with arthritis or other inflammatory conditions. Because of its anti-inflammatory effects, however, aspirin is also indicated for treatment of inflammation associated with rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, spondylarthropathies, and arthritis and pleurisy associated with systemic lupus erythematosus (SLE) (FDA,

1998). One mechanism of aspirin's anti-inflammatory effect is peripheral inhibition of the COX-2 enzyme. Expression of COX-2 is augmented 10-20 fold by inflammatory cytokines. In addition, other mechanisms unique to NSAIDs may contribute aspirin's anti-inflammatory effects.

8.4.3.4 Cardiovascular

Aspirin is unique in its beneficial cardiovascular effects. Aspirin is currently approved to reduce the risk of recurrent ischemic stroke and stroke after transient ischemic attack (TIA), for suspected acute myocardial infarction (MI), prevention of recurrent MI, unstable angina pectoris, chronic stable angina pectoris, and for use in some revascularization procedures in selected patients (FDA, 1998). A recent statement from the US Preventive Services Task Force provides strong support for use of aspirin in primary prevention of heart attacks (USPSTF, 2002), an indication that is not yet approved by the FDA. Likewise, while the indication is not currently approved by the FDA, aspirin may also be effective in reducing the *severity* of both stroke (Wilterdink, 2001) and myocardial infarction.

Although aspirin demonstrates a dose response relationship for pain relief for doses between 300-1000 mg, increasing dose does not enhance benefit in cardiovascular disease prevention. A meta-regression analysis suggests that the beneficial effect on the incidence of stroke is uniform across aspirin doses between 50 and 1500 mg/d. The apparent absence of a dose-response effect over this dose range (Johnson, 1999) may reflect the complete and irreversible acetylation of platelet cyclooxygenase that occurs at low doses.

Due to the apparent confusion regarding the differences between ingredients, many consumers mistakenly take non-aspirin-containing products such as acetaminophen instead of aspirin for intended cardiovascular disease prevention. A survey of 40,000 US households found that 23% of the people taking an analgesic for cardiovascular prevention report taking a non-aspirin product like acetaminophen or ibuprofen (Heart Information Network, 2001). In fact, the results showed that Tylenol® (acetaminophen) is taken as frequently as the leading brand of enteric coated aspirin for the prevention of a second heart attack (16%). Other non-aspirin products reportedly being taken for cardiovascular protection included ibuprofen (18%) and naproxen sodium (5%) (Heart Information Network, 2001). These survey results highlight the confusion over the therapeutic benefits of aspirin versus other analgesics, and highlight the need for stronger ingredient-specific labeling and patient education.

8.5 Safety Overview

An analysis of the side effect profiles of OTC aspirin and acetaminophen, through single and multiple dose clinical trials, clinical observation and adverse event reporting systems, demonstrates that both agents when used according to the approved labeling are safe and effective. Each ingredient, however, can be associated with *specific* adverse reactions,

which will be discussed in detail in this section. Differences in susceptible populations and contraindications for use highlight the need for ingredient specific product labeling that would inform high-risk populations of ingredient-specific adverse reactions and improve consumer protection.

8.5.1 Mechanism of Action

A drug's mechanism of action may explain its adverse event profile as well as its therapeutic benefits. In particular, toxicities involving the kidney, liver and gastrointestinal systems can often be predicted based on the mechanism of action and/or metabolic processing of the drug. Table 14 summarizes the mechanisms of action of aspirin and acetaminophen that may be associated with particular adverse events.

Table 14: Major Adverse Events and Mechanism of Action

	Aspirin*	**Acetaminophen**
Potential Adverse Effect	GI injury and bleeding	Hepatotoxic injury
Mechanism of Action	Inhibition of COX-1 (consequence of mechanism of action)	Metabolic Elimination Pathway (consequence of metabolism)

* Green, 2001

Inhibition of prostaglandin synthesis by aspirin has been implicated in causing gastrointestinal (GI) adverse reactions (Stiel, 2000), including, in rare cases, pastric perforations, ulcers and bleeding. Aspirin has been shown to affect neutrophil adherence, thus increasing the risk of mucosal injury. At the superficial mucosal level, aspirin is a weak acid. In the highly acidic environment of the stomach, however, aspirin is non-ionized and able to migrate across cell membranes into the superficial epithelium where it is metabolized. In its ionized form, aspirin traps hydrogen ions and can attenuate the protective effects of gastric mucosa, leading to epithelial damage (Green, 2001).

The gastrointestinal effects of chronic, high dose aspirin use are linked to prostaglandin inhibition, the mechanism responsible for its analgesic and anti-inflammatory effects. Acetaminophen is not generally believed to be associated with a high risk of similar gastrointestinal effects. Recent study data, however, suggest that acetaminophen (1000 mg) may exert a weak, reversible isoform nonspecific COX inhibitory action (Catella-

Lawson, 2001), thus suggesting the potential risk of GI effects following a similar mechanism of action as that of aspirin.

Despite these preliminary data, it is generally held that adverse effects related to acetaminophen, including hepatotoxicity, are not linked to its mechanism of action. Rather, hepatotoxicity is a consequence of acetaminophen's metabolic elimination pathway.

8.5.2 Preclinical Studies

Preclinical studies of the effects of aspirin and acetaminophen in animal models have been conducted to evaluate the safety of these ingredients. These studies have been described in detail in a review by Dr. Helen Northroot (NorthRoot, 2001). While clinical findings should be viewed as more meaningful for ingredients that have been widely used for extended periods of time, for completion, a short summary of pertinent animal findings is provided.

It is difficult to produce serious hepatotoxicity in preclinical studies with aspirin as GI effects are dose-limiting in intact animal models. Under these conditions serious hepatotoxicity does not occur. Thus, it is only possible to demonstrate effects on clinical markers of liver injury, including changes in liver enzyme levels, liver collagen content, alterations in glutathione levels (Micheli, 1992), and cellular cytotoxicity (Sorenson, 1985). On the other hand, acetaminophen-induced hepatotoxicity has been established in a series of animal models (Savides, 1984; National Toxicology Program 1993; Villar, 1998).

Gastrointestinal effects of aspirin are widely reported in animal studies (Hallesy, 1973; Thomas, 1977). GI effects with acetaminophen are not generally observed in animal studies (Thomas, 1977).

Nephrotoxicity from aspirin is highly species-dependent (Bach, 1985; Bach, 1998; Schnellmann, 1998). Large doses of acetaminophen are likely to induce acute kidney necrosis in most mammalian species (Mugford, 1997). Based on the preclinical data, it can be concluded that both aspirin and acetaminophen have the potential to induce renal damage, following overdose.

Aspirin is known to prolong bleeding time due to inhibition of platelet function. Alternatively, the effects of acetaminophen on the blood, including methemoglobinemia (Savides, 1984) and mononuclear cell leukemia (National Toxicology Program, 1993), have been noted in animal models.

While hypersensitivity reactions are well-documented in humans, preclinical studies addressing this adverse effect in animals are not conclusive. Clinical allergic reactions noted in humans are idiosyncratic and difficult to simulate in animal models.

Animal data suggest that salicylates are teratogenic (Karabulut, 2000), while acetaminophen may interfere with spermatogenesis and fecundity (Reel, 1992).

8.5.3 Comparative Safety of Aspirin and Acetaminophen

As with all drugs, OTC analgesics can be associated with adverse reactions. In comparing safety of specific drug ingredients, it is important to compare similar usage patterns (i.e., single-dose or multiple dosing), as dosing frequency and duration affect adverse event profiles. Based on data from the diversity of studies involving over 26,000 patients in observational, case-control, randomized controlled trials, and meta-analyses, aspirin and acetaminophen at both single and multiple OTC dosing schedules demonstrate almost equivalent safety profiles in terms of total adverse events (Cooper, 1985; Autret, 1997; Elfström, 1999; Fries, submitted, 2002). These data, highlighted in Table 15, clearly support the safety of aspirin and acetaminophen for OTC use.

Table 15: Comparative Safety of Aspirin and Acetaminophen

Study/Adverse Event	Patients Reporting Adverse Events (%) Aspirin	Acetaminophen	Placebo
Single Dose Studies			
Cooper (1985)	**325 mg-1300mg (n=927)**	**500-2000 mg (n=789)**	**(n=1968)**
GI Events			
Nausea	2.48	1.90	2.85
Vomiting	0.76	0.63	0.51
CNS Events			
Drowsiness	9.71	10.90	5.64
Dizziness	2.48	1.87	2.97
Lightheadedness	1.40	0.27	0.42
Disorientation	0.11	0.00	0.10
Allergy Events			
Rash	0.43	0.13	0.10
Skin Irritation	0.00	0.13	0.00
Eyes Burning (Watery)	0.11	0.25	0.05
Elfström (1999)	**800 mg (n=201)**	**1000 mg (n=200)**	**(n=200)**
GI Events	28	23	25
Multiple Dose Studies			
Moore (1999)	**≤3000 mg/day (n=2900)**	**≤3000 mg/day (n=2888)**	
All Adverse Events	18.7*	14.5*	
Singh, 2000	**(n=4164)** †		
GI Events	Aspirin > Acetaminophen*		
Fries, submitted, 2002	**(n=8816)** †		
GI Events	Aspirin=Acetaminophen		

*Statistically significant difference

† Includes patients exposed to OTC analgesics including aspirin, acetaminophen, ibuprofen or naproxen sodium

8.5.3.1 Adverse Event Profile

In comparing safety data of different drugs, it is important to consider the pattern of use. Physician-monitored, high-dose aspirin regimens used for inflammatory relief are associated with a higher frequency of side effects than lower dose OTC regimens. In a comparative study of NSAIDs most frequently used for rheumatic disorders, aspirin was one of the most effective and the best-tolerated treatments (however, this may reflect differences in dosing or formulations) (Fries, 1993). Despite the incidence of side effects, the benefit to risk relationship for both professional and OTC uses is considered favorable due to the level of benefit achieved (Fries, 1993; Weisman, 2002).

Comparative studies evaluating the overall safety profiles of aspirin and acetaminophen suggest that both ingredients are associated with similar risk profiles (Cooper, 1985; Autret, 1997). In a retrospective meta-analysis of 3700 patients in 54 single-dose aspirin (325-1300 mg) or acetaminophen (500-2000 mg) dental pain studies, occurrences of drug-induced side effects did not differ from a placebo control group (Cooper, 1985). In this analysis, only nausea was reported with any frequency; however, compared to the 2.85% of the placebo patients, nausea occurred in only 1.9% of the acetaminophen patients and 2.48% of the aspirin patients (Cooper, 1985). Likewise, a comparison study of equal doses of aspirin or acetaminophen, or ibuprofen (7.5-30 mg/kg) in children, suggest that the safety profile of aspirin and acetaminophen were equivalent, and both were better tolerated than ibuprofen (Autret, 1997).

A double-blind randomized clinical study of multiple, short term dosing (maximum of seven days of treatment) of acetaminophen, aspirin, and ibuprofen, compared the rate of "significant" adverse events among these ingredients. A total of 8677 patients, distributed approximately equally in the three treatment arms, were administered aspirin or acetaminophen (doses up to 3000 mg daily), or ibuprofen (1200 mg/day) for short-term management of mild to moderate pain for common conditions. At least one adverse event was reported in 18.7% of patients on aspirin and 14.5% of patients receiving acetaminophen. These findings demonstrate the safety of aspirin and acetaminophen, and the absence of meaningful adverse effects under the study conditions

While there is an abundance of safety data for high-dose aspirin used to treat rheumatic conditions under a physician's guidance, there are limited data on the safety of high-dose, OTC-compliant aspirin use. However, recent data from three pooled migraine efficacy studies evaluating the safety of 1000 mg aspirin compared to placebo demonstrate that maximum OTC doses of aspirin do not increase the risk of serious adverse clinical events (Bayer NDA 21-317) (Table 16). It should be noted that as with most clinical trials, these comparison studies did not include patients with certain underlying conditions that may increase risk of adverse events.

Table 16: Adverse Reactions Reported by Body System to 1000 mg Aspirin Compared with Placebo

Adverse Reactions	Aspirin (1000 mg)* (N=596)		Placebo** (N=595)	
	Number	%	Number	%
Subjects Reporting One or More Events	65	11	50	8
System Organ Class				
Body as a whole	13	2	15	3
Cardiovascular	2	0	5	1
Digestive System	30	5	18	3
Nervous System	20	3	11	2
Respiratory System	0	0	1	0
Skin	2	0	3	1
Special senses	7	1	6	1

* Two, 500 mg unbranded aspirin caplets

** Two, 500 mg matching placebo caplets

8.5.3.2 Gastrointestinal Events

The development of GI mucosal changes has been consistently observed with OTC aspirin and other NSAID use. Endoscopic studies have examined the extent of GI mucosal changes following acute or chronic analgesic exposure, and have identified evidence of the appearance of superficial lesions or petechiae. Studies examining the GI effects of analgesic formulations at OTC doses suggest that enteric-coated aspirin is associated with a lower degree of endoscopically visible lesions than uncoated aspirin (Lanza, 1984; Lanza, 1975), and acetaminophen is associated with minimal mucosal lesions. The clinical significance of endoscopically visible lesions has been questioned, however, as such effects do not necessarily correlate with risk of bleeding, ulceration, or other untoward effects including subjective symptoms. Endoscopic studies linking the extent and degree of acute mucosal injury to aspirin and various analgesics have limited value in predicting the frequency or severity of chronic gastric ulcers or gastrointestinal bleeding (Graham, 1986).

Because of its low risk for producing ulceration, ibuprofen is often considered the reference compound for determining the relative risk of GI events with chronic dosing (relative risk of 1.0). Aspirin at OTC doses has been associated with an increased risk of GI events, with a relative risk ranging from 2.6 to 5.8 (Kelly, 1996), and acetaminophen

is generally regarded as not inducing risk of GI injury. Despite these typical characterizations, a recent analysis of the ARAMIS database, a post-marketing surveillance program and National Arthritis Data Resource, suggests that the risk for GI injury due to aspirin or ibuprofen use in "low-risk" subjects (including rheumatoid arthritis patients) does not differ from the risk associated with acetaminophen use, and that the risk is also similar to that of background rates (Fries, submitted, 2002).

Serious GI complications requiring hospitalization occur at an annual rate of 1-2% in individuals who take *prescription* NSAIDs regularly (Cryer, 1999), and recent data suggest that the rate of hospitalization for NSAID-related serious GI complications has decreased over time (Singh, 1999). However, caution is warranted when assessing the risk of OTC-compliant dosing based on prescription use patterns. In light of risks associated with OTC use, product labeling, as bolded below, adequately warns consumers about aspirin use under certain risk conditions.

Do not take this product if you are allergic to aspirin, have asthma, have stomach problems (such as heartburn, upset stomach or stomach pain) that persist or recur, gastric ulcers or bleeding problems unless directed by a doctor.

Unlike aspirin-containing products, acetaminophen is not generally associated with GI events and is not requited to carry similar labeling. Despite the suspected low risk of GI events with acetaminophen use, there are limited epidemiologic data evaluating GI risk and acetaminophen. Recent data suggest that daily doses of acetaminophen $\geq$ 2000 mg are associated with increased risk of GI complications, particularly when acetaminophen is taken concomitantly with other NSAIDs (Rahme, 2000; Garcia Rodriguez, 2001). These studies suggest an interaction or augmentation of cyclooxygenase inhibition when NSAIDs are taken together with acetaminophen (Garcia Rodriguez, 2001).

A double-blind randomized clinical study of multiple, short term dosing (maximum of seven days of treatment) of acetaminophen and aspirin further highlights the potential for GI injury with acetaminophen use (Moore, 1999). In this study, 4 patients in the acetaminophen group and 2 patients in the aspirin group reported non-serious gastrointestinal bleeding. Additionally, there was one case of peptic ulcer with aspirin use. Following an analysis of organ systems, "body as a whole," "digestive system," "abdominal pain," "dyspepsia" and "nausea" were identified more frequently in the aspirin group. However, acetaminophen users reported dyspepsia and all digestive events significantly more frequently than a comparative ibuprofen group.

The long-term effects of acetaminophen use on gastrointestinal injury have not been adequately studied, warranting the need for future investigations. In particular, the effects of acetaminophen in patients concurrently taking NSAIDs, or in patients with previous peptic ulcers needs further evaluation. Likewise, further study is needed to better quantify the purported association of analgesic use and gastrointestinal effects, particularly since many reports may be the result of significant recall bias against the NSAIDs, especially aspirin. Failure to probe for acetaminophen use in GI injury cases may lead to an inaccurate assessment of its GI risk.

The risk of GI toxicity is dependent on both dose and duration, and the overall risk is greater with use of more than one anti-inflammatory drug taken simultaneously (Stiel, 2000; Garcia Rodriguez, 2001; Fries, submitted, 2002). Cameron (1975) demonstrated an exponential increase in the relative risk of developing a chronic gastric ulcer relative to the number of self-reported aspirin tablets consumed per week (the vast majority of tablets were regular strength (325 mg) used for pain relief).

In addition to dose, duration, and concomitant medications, increasing age, co-morbid conditions, and presence of *H. pylori* infection may also contribute to the development of an adverse event (Stiel, 2000). These factors may affect the body's ability to metabolize drugs properly or can interfere with the pharmacokinetic properties. Previous peptic ulcer is a known risk factor for aspirin or NSAID-induced gastric ulcer or GI disturbances. In fact, the prevalence of gastric ulcers is 32.6% in patients with a history of gastric ulcer and is more than twice that of patients with no GI history (13.5%), including previous gastric ulcer, duodenal ulcer, or upper GI hemorrhage (Cheatum, 1999). Evidence also suggests that there may be an increased risk of gastric injury from the combination of aspirin and NSAIDs with the addition of alcohol (Peura, 1997); however these data are preliminary and require further validation.

Patients with bleeding disorders or significant cardiovascular disease may also be at an increased risk for GI disorders or may have an impaired ability to tolerate NSAID-induced gastrointestinal adverse reactions. However, while patients with cardiovascular disease may be at increased risk of GI adverse effects of aspirin use, data suggest that benefits of aspirin outweigh the risk of aspirin-induced GI events. A recent meta-analysis of six trials (6,300 patients) meeting the inclusion requirement of aspirin in a dose of $\leq$ 325 mg/day in approved secondary prevention of myocardial infarction indications found that aspirin reduces all cause mortality and that 1-5 deaths can be prevented for every manageable GI event caused (Weisman, in press, 2002). In this context, the benefits of aspirin clearly outweigh the risks.

8.5.3.3 Hepatic Events

At OTC-compliant doses, aspirin has rarely been implicated in chronic, long-term hepatic toxicity. Studies of patients receiving prescription doses of analgesics have documented elevations in liver enzymes; however, these increases rarely progress to liver failure with aspirin use (Lewis, 1998). The risk of acute, intrinsic hepatotoxicity increases with high blood levels of the drug, and is significantly related to preexisting hepatic impairment, juvenile arthritis, rheumatic fever, or SLE (Zimmerman, 1990).

Irreversible hepatic failure, on the other hand, is more commonly associated with acetaminophen use (Ostapowicz, 2000). In a recent study, acetaminophen was the most common cause for drug induced acute liver failure in the United States between January 1998 and October 2000; accounting for 38% of all cases (Lee, 2001). Remarkably, acetaminophen is the single most common etiology for acute liver failure in the United States, Europe and Australia (Lee, 2001).

Acetaminophen hepatotoxicity is dose-dependent and usually associated with overdose. However, hepatotoxicity has been reported in susceptible individuals taking therapeutic OTC doses (McClain, 1999). Acetaminophen is metabolized to a toxic metabolite, N-acetyl-p-benzoquinone-imine (Gilman, 1996). Normally this metabolite combines with hepatic stores of glutathione preventing liver cell injury. When glutathione stores are depleted due to overproduction of this metabolite (due to excessive doses, alcohol consumption or other underlying conditions), the metabolite can bind to liver cell proteins causing hepatic necrosis (McClain, 1999).

While high doses of acetaminophen can result in increased levels of the toxic metabolite, there are several other factors suspected to increase the risk of acetaminophen toxicity with normal therapeutic use (Prescott, 2000). Dose, body weight, age and individual metabolic rates are known factors that influence adverse drug reactions.

The metabolism of acetaminophen differs between children (under the age of 12) and adults, with sulfate or glucuronide conjugation being the dominant route of elimination in children and adults, respectively (Miller, 1976). This metabolic difference between adults and children may explain why children are less susceptible to hepatotoxicity after an overdose of acetaminophen (Rumack, 1986; Kumar, 1990). However, the American Academy of Pediatrics warns that some conditions, including obesity, diabetes, malnutrition and some viral infections, can make children more vulnerable to toxicity (American Academy of Pediatrics, 2001).

In addition to body size and age, genetic differences, diet, nutritional state and fasting can influence acetaminophen toxicity. Individuals at increased risk for acetaminophen toxicity include patients with Gilbert's syndrome, and patients with deficient glucuronide conjunction that leads to increased production of the toxic metabolite of acetaminophen (Esteban, 1999). Studies suggest that fasting may also increase risk of acetaminophen hepatotoxicity by reducing glutathione synthesis and glucuronide and sulfate conjugation (Price, 1987). As discussed later, various drug interactions may also increase the risk of hepatotoxicity.

While the factors mentioned are likely to influence acetaminophen toxicity, much concern has been raised regarding chronic alcohol abuse and the increased risk of liver toxicity from excessive acetaminophen use (Dragonov, 2000; Zimmerman, 1995), particularly during fasting (Whitcomb, 1994). There are several hundred reports of untoward effects with alcohol and acetaminophen in the published literature; however these reports span more than twenty years. Thus, the actual incidence, while of clinical interest and concern due to its severity, is relatively small compared to the number of users of acetaminophen.

Although two clinical studies have attempted to demonstrate a lack of correlation between alcohol intake and acetaminophen-induced liver damage (Dart, 2000; Kuffner, 2001), pharmacological studies consistently demonstrate that the metabolism of acetaminophen increases in chronic alcoholism (Girre, 1993, Thummel, 2000). Data supporting the role of alcohol to increase the risk of acetaminophen hepatotoxicity, along with several case reports of acetaminophen- and alcohol-induced hepatotoxicity,

prompted the FDA to establish a final rule requiring all non-prescription analgesic products to have a label warning consumers of the interaction of alcohol and OTC analgesic products (FDA, 1998). While this alcohol warning highlights the potential adverse reaction interaction, it falls short in warning consumers of the unique risk of hepatic injury with acetaminophen use by blanketing all OTC analgesic products.

A recent study investigated the relationship between alcohol and acetaminophen to determine if hepatic injury occurred with maximal therapeutic dosing of acetaminophen to chronic alcohol abuse patients immediately following cessation of alcohol (Kuffner, 2001). This study found that repeated doses of acetaminophen administered after the elimination of alcohol was not associated with evidence of liver injury (Kuffner, 2001). The study design and study population, however, suggest that the data may not accurately reflect the risk of acetaminophen toxicity in chronic alcohol users. Half of the study population had been actively drinking for 4 weeks or less, with half of these people drinking for less than one week; thus excluding chronic alcoholics who are likely to be at high risk for acetaminophen toxicity. Based on the short duration of alcohol exposure in the majority of the study population, it is plausible that alcohol intake was not sufficient to induce increased toxicity with acetaminophen. Additionally, the patients in this study were given 8 g of acetaminophen over a 48-hour period, a test condition that does not evaluate the risk of repeated exposure to acetaminophen over time in chronic alcoholics. During administration of the test agent, the patients were well-fed, thereby eliminating further depletion of glutathione and increased risk of toxicity induced by fasting, a common nutrition state of alcoholics (Soll, 2002).

Physicians and other clinicians need to be aware of the possible association between hepatotoxicity and acetaminophen and alcohol use. Awareness is particularly important as the initial clinical presentation of acetaminophen toxicity in chronic alcoholics has distinct symptoms from acetaminophen hepatotoxicity due to overdose or alcohol-induced hepatitis (Kumar, 1991). Physician awareness is imperative as early diagnosis and treatment are crucial to decrease overall mortality (Dragonov, 2000; Zimmerman, 1995).

8.5.3.4 Renal Events

Normal renal function, which is dependent on prostaglandin synthesis, can be adversely affected by drug-induced inhibition of the renal COX enzyme (Crofford, 2000). Aspirin use, therefore, may interfere with renal function due to its action on the COX enzyme system. Elevations in blood urea nitrogen or serum creatinine levels have been noted with long-term, high dose aspirin use (Bonney, 1986), as well as short-term use in patients with underlying renal impairment (Whelton, 1990). Cessation of aspirin use, however, typically results in a reversal of the noted drug-induced effects on renal function (Bonney, 1986; Whelton, 1990).

A unique type of renal toxicity, analgesic nephropathy, has been associated with both aspirin and acetaminophen, however such toxicity is most often seen only after years of

exposure to high therapeutic doses or mixtures containing at least two antipyretic analgesics with caffeine or codeine (De Broe, 1998). Many initial reports of analgesic nephropathy described patients taking large amounts of products containing phenacetin (De Broe, 1998). These have been removed from the US market.

While the risk of analgesic-induced renal toxicity is low, pre-existing conditions that may increase the risk, such as diabetes (Whelton, 1991), concomitant diuretic therapy, renal or hepatic impairment, cardiac failure, or old age, suggest that caution is warranted against indiscriminate use of non-prescription dosages. Data suggest that short-term, OTC dose compliant treatment is not associated with a high risk of renal toxicity, even in the presence of underlying renal or hepatic impairment. To further reduce the risk, OTC product labeling urges patients to seek the advice of a physician before using a product if any of the above-mentioned conditions are present.

8.5.3.5 Circulatory and Cardiovascular Events

Due to anti-platelet effects, patients with coagulation defects, such as von Willerbrand's disease, hemophilia, thrombocytopenia, uremia and cirrhosis, should avoid aspirin containing products. Similarly, those who take anticoagulants should not use these ingredients unless directed to do so by a physician.

Acetaminophen is generally recognized as a safe alternative for patients with underlying conditions that affect coagulation (Hylek, 1998). However, it should be noted that hepatic disease could be the cause of coagulation defects. Thus, these patients should use acetaminophen cautiously, as the risk of hepatotoxicity due to overdose may affect coagulation. Likewise, recent reports suggest that acetaminophen may increase anticoagulation in patients who are taking warfarin (Lehmann, 2000), (Andrews, 2002).

8.5.3.6 Hypersensitivity Reactions

Some patients with asthma may experience potentially life-threatening hypersensitivity reactions to aspirin (Settipane, 1983). Although the mechanism of aspirin intolerance is unknown, it is hypothesized that the majority of allergic complaints are due to drug-induced inhibition of COX production, which causes arachidonic acid to be metabolized through the lipoxygenase pathway rather than the cyclooxygenase pathway (Szczeklik, 1983). As a result, leukotrienes, which can cause bronchospasm and anaphylaxis, accumulate, thus initiating sensitivity reactions (ASHP, 1999). Patients with a history of nasal polyps or aspirin-induced disorders such as severe rhinitis, sinusitis, urticaria, angioedema, bronchospasm, or anaphylaxis should avoid aspirin.

In light of the potential hypersensitivity reactions with aspirin use, the following label is included on aspirin-containing products:

Do not use if you are allergic to aspirin or any other pain reliever/fever reducer.

Although acetaminophen is often recommended as an alternative treatment for aspirin-sensitive patients, sensitivity has been reported in as many as 34% of aspirin-sensitive asthmatic patients receiving average OTC doses of acetaminophen (Settipane, 1995). While the reported hypersensitivity reaction to acetaminophen is generally not as severe as aspirin-induced reactions, asthma sensitization is not a unique attribute to aspirin (Settipane, 1995). Acetaminophen and aspirin have both been associated with allergy, anaphylaxis, urticaria, asthma and bronchospasm, rashes, and rarely, Stevens-Johnson syndrome.

8.5.3.7 Uric Acid Metabolism

It is recommended that aspirin be avoided during acute gout attacks (American College of Rheumatology, 2001), as daily dosages of 1-2 g inhibit tubular secretion or uric acid and elevate plasma urate concentrations, which may worsen hyperuricemia (Lipman, 1996) or antagonize the uricosuric effects of some drugs (probenecid and colbenemid) commonly prescribed for the treatment of gout or hyperuricemia (Lipman, 1996). These adverse effects, however, are usually only seen with chronic physician-monitored dosing, and OTC aspirin may be used safely under doctor's care for short-term treatment of acute gout (American College of Rheumatology, 2001). Acetaminophen does not interfere with uric acid secretion, and does not present risk in patients with gout or hyperuricemia.

8.5.3.8 Adverse Effects in Special Populations

Children

Aspirin has been shown to be an effective antipyretic agent in children (Yaffee, 1981), however, several case reports and case-control studies have associated Reye's syndrome with salicylate use in children suffering from specific viral infections. While the true cause of this syndrome of acute encephalopathy and liver disease in children under 17 years of age is unknown, it may involve inborn errors of metabolism. Reye's syndrome is a serious disease, as it progresses to death in 80-90% of the cases. Therefore, to eliminate possible aspirin-induced cases of Reye's syndrome, it is recommended that aspirin *not* be administered to any child suffering from flu-like symptoms or any other viral illnesses, including chicken pox (Desjardins, 1998).

The suspected link between aspirin and Reye's syndrome influenced the FDA to mandate Reye's syndrome labeling on salicylate-containing products. The Reye syndrome-warning label, noted below, represents an example of ingredient-specific labeling, which many suggest led to the dramatic reduction in the occurrence of Reye's syndrome in the United States (Belay, 1999; Committee on Infectious Disease, 1982).

Children and teenagers should not use this medicine for chicken pox or flu symptoms before a doctor is consulted about Reye's syndrome, a rare but serious illness reported to be associated with aspirin.

Based on the suspected causal relationship between aspirin and Reye's syndrome and the similar mechanism of action of aspirin and the other OTC analgesics (NSAIDs), acetaminophen has become the most commonly used analgesic/antipyretic in children in the United States (Prescott, 1996). While case reports and studies suggest that aspirin increases the incidence of Reye's syndrome, concomitant use of acetaminophen (Autret-Leca, 2001) or anticonvulsants with aspirin, as well as acetaminophen use in the absence of aspirin (Orlowski, 1990), have also been implicated in some cases Reye's syndrome.

The decrease in aspirin use and corresponding increase in acetaminophen use due to the suspected risk of Reye's syndrome with aspirin use may be a contributing factor to the increasing prevalence of asthma, atopic eczema, and allergic rhinitis in children of Western countries, including the United States, where acetaminophen is favored over aspirin (Varner, 1998). This hypothesis is based on the biologic effects of cytokines and prostaglandins on allergic sensitization and the differing mechanisms of action of aspirin and acetaminophen (Varner, 1998).

Due to current practices of administering acetaminophen to children, the American Pediatrics Academy warns that children are at greater high risk for acetaminophen overdose (American Pediatrics Academy, 2001). As for many drugs, the usual dose of acetaminophen is based on body size, with a much lower dose recommend for children than for adults (160-480 mg/dose for children ages 2-12 versus 500-1000 mg/dose for adults). Despite these dosing recommendations, a study of reported cases of acetaminophen hepatotoxicity in children found that 52% of the children received adult preparations of acetaminophen (Heubi, 1998). Of the children reported in these cases, 55% died of hepatic failure, and 3 patients survived only after liver transplantation. The risk of acetaminophen toxicity in children is exacerbated by the lack of awareness of the potential toxicity due to overdose, and the fact that there are multiple children's products, which contain acetaminophen, increasing the chance of unintentional overdose.

Pregnant Women

Women are advised to avoid most drugs during pregnancy due to possible developmental effects on the fetus. Aspirin, in particular, should be avoided in the third trimester because of its ability to inhibit labor and prolong pregnancy by inhibition of prostaglandin synthesis (Schoenfeld, 1992). Based on this interaction, a prominent pregnancy warning is included on aspirin products:

As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product. It is especially important not to use aspirin during the last three months of pregnancy unless specifically directed to do so by a doctor, because it may cause problems in the unborn child or complications during delivery.

Due to FDA-mandated labeling warning against aspirin use during pregnancy, OTC doses of acetaminophen have generally been considered the safest choice for managing minor pain and fever in pregnant women (Briggs, 1993; Balligan, 1993). However, the FDA does warn consumers to use caution with concomitant drug use. The following label is included on all acetaminophen-containing products:

As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product.

While acetaminophen is widely used, long-term safety of drug use in the mother and child has not been assessed. Alternatively, recent studies support the safe use of aspirin in pregnant women despite the recommendation to avoid aspirin in the third trimester of pregnancy (Hayes, 1981). The Collaborative Low Dose Aspirin in Pregnancy (CLASP) Study demonstrated that there is no significant maternal or fetal risk from low doses of aspirin used to avert pregnancy-induced hypertension (CLASP, 1994). Furthermore, long-term follow-up (12-18 months) studies demonstrate that aspirin use does not induce adverse effects on child development (Imperiale, 1991; CLASP, 1995). Recent findings have also suggested that low-dose aspirin offers beneficial effects for women at high risk of early onset pre-eclampsia (CLASP, 1995), and low-dose aspirin in combination with heparin has been shown to be beneficial for women with recurrent pregnancy loss (Lee, 2000).

Elderly

Elderly patients are generally at greater risk for drug-drug and drug-disease interactions with analgesics because they often take numerous medications to treat chronic conditions (Erwin, 1995). Specific drug-drug interactions with aspirin and acetaminophen will be discussed later. Aspirin-induced gastropathy, renal impairment, hypersensitivity, and prolonged bleeding are common in older persons. Of particular concern in the elderly are the gastrointestinal side effects of aspirin (Kennedy, 1997). It has been reported that elderly patients who take NSAIDs, including aspirin, are almost five times as likely to die from gastrointestinal bleeding than those who do not (Griffin, 1988). While many elderly patients take low dose aspirin for its cardiovascular benefit, the benefits of aspirin use have been shown to outweigh the risk of GI events in appropriately treated patients (USPSTF, 2002).

The elderly population may be more susceptible to adverse events to aspirin as a result of age-related pharmacokinetic changes involving protein binding (Erwin, 1995). Aspirin is

highly protein bound (≥90%); however, because serum albumin levels tend to be lower in elderly patients, there is a higher free fraction of aspirin in the blood. This increase in unbound or free fractions of the drug in elderly patients may enhance the clinical effect of pain relief, but may also increase risk for toxicity (Murray, 1990).

8.5.4 Post Market Surveillance

Recent post-marketing reports of acetaminophen-induced hepatotoxicity caused the FDA to raise concerns regarding the safety of acetaminophen and other marketed analgesic ingredients.

Post-marketing surveillance and risk assessment programs are useful in identifying adverse events that may not have been identified during clinical development or in the literature. Spontaneously reported adverse event data are useful in identifying signals that may potentially effect the safe use of the product. However, due to the limitations of spontaneous report data, controlled investigations are required to appropriately quantify risk. If the investigations demonstrate that there is a significant risk, measures, such as revised labeling, can be implemented to optimize safe use of the product. In certain situations, these measures have included a re-evaluation of the approval or marketing decision.

The interpretation and usefulness of spontaneous adverse event report data in assessing risk is limited by a number of factors. Reports, particularly those from consumers, are often incomplete or data are of poor quality making it difficult, if not impossible, to establish if an agents is associated with the event. Key information, such as dose and duration, concomitant medications, co-existent diseases, patient history, demographic information, may not be available for accurate case assessments. Establishing the true adverse event rate is difficult due to the inadequate information to precisely determine drug exposure, especially in the OTC setting. Also, reporting rates can be influenced by reporting biases or media influence and therefore, are not reliably reflective of incidence.

8.5.4.1 FDA Case Reports for Acetaminophen Hepatic Events

FDA had identified 307 cases of liver injury associated with acetaminophen ingestion from 1998-July 2001. Of these, 282 reports involved adults. Approximately 60% of these cases involved severe life threatening injury with liver failure and approximately 44% resulted in death. Reports were categorized by severity of the injury:

- very mild/poorly characterized (category 1)
- mild to moderate injury (category 2)
- moderate to severe (category 3)
- severe life threatening injury with liver failure (category 4)

Case severity followed a dose-response relationship. The estimated median daily doses were 6.0g, 5.85 g, 4.2 g, and 4 g for reports in categories 4, 3, 2 and 1, respectively. The

OTC maximum daily dose for acetaminophen is 4 g. There were 26 cases classified as category 4 where the daily dose was estimated at less than 4g. However in 18 of these cases, other factors such as underlying hepatic disease or alcohol abuse were also reported.

In over 75% of the cases only one acetaminophen-containing product was used. Where product category was specified (227cases), 53.7% involved a prescription narcotic analgesic combination product and 33.5% involved a single ingredient acetaminophen product, while less than 12% involved an OTC combination product.

As expected, the mean or median dose of acetaminophen producing liver injury was lower for individuals with underlying hepatic disease, concomitant alcohol consumption and concomitant administration of other hepatotoxic drugs.

In summary, the OTC labeling for acetaminophen-containing products provides for a 4 g daily dose and warns consumers who consume alcohol or have underlying liver disease to consult a physician prior to use. The use of OTC combination products was cited in only a small proportion of cases. New labeling guidelines have recently been implemented on all Bayer acetaminophen containing products to better inform consumers about the active ingredients, the appropriate dosing and to minimize the potential for inappropriate multi-product use.

8.5.4.2 FDA Case Reports for Aspirin GI Events

FDA has cited 541 cases of significant GI adverse events spontaneously reported for aspirin from 1998 through 2001. Of these reports, the indications for use were established in 305 cases and, since some patients (no more than 11) used aspirin for multiple indications, a total of 316 indications were identified. These can be categorized into one of two groups: vascular and non-vascular. The vascular category includes heart disease, CAD, cerebrovascular disease, non-cardiac vascular thrombosis, occlusion and stent placement, while the non-vascular category includes pain, headache, migraine, arthritis, flu/fever symptoms and miscellaneous indications. We have assumed that where the product was used for multiple indications, one indication was in the vascular category.

There are 210 case reports (68.9% of cases for which an indication was identified) where aspirin was used for a vascular indication. Non-vascular indications were assigned for the remaining 95 cases (33.1%). Not only is the number of reports significantly higher for the vascular indication category, but, using sales volume as an estimate for exposure, the report rate for vascular use is more than twice the rate for non-vascular use, as shown in the Table 17.

Table 17. Aspirin : FDA Gastrointestinal Events, 1998-2001

	# CASES	%	SALES *	RATE (#CASES/BILLION SOLD)
Vascular indications	210	68.9	27.8	7.55
Non-vascular indications	95	31.1	33.1	2.87
Total (cases with known indication)	305			

* Unit sales volume in billions of aspirin containing tablets, 1998-2001 total

This relatively larger number and rate of vascular cases is not unexpected when one considers the populations involved and exposure time with the use of aspirin for vascular indications compared to non-vascular indications.

The population taking aspirin for vascular indications, such as prevention of a second heart attack, have significant cardiovascular disease, are more likely to be elderly, to have co-morbidities and to take other medications. The use of aspirin in cardiovascular disease is approved only under the care of a physician, so that therapy can be monitored appropriately. While there is a certain risk associated with daily dosing for cardiovascular indications, the life saving benefits are clearly recognized to outweigh this risk.

Use for nonvascular indications is a closer approximation to OTC consumer use, the intermittent treatment of mild to moderate pain or for fever reduction. In the OTC setting appropriate dosing is indicated in the labeling, and limitations for the duration of use are specified. As noted above, less than one third of the case reports identified by the FDA were associated with OTC use.

8.5.4.3 Poison Control Center Data

Clearly both aspirin and acetaminophen can cause adverse events. Acetaminophen overdose has been associated with significant hepatotoxicity and death. While severe GI events have been reported with the nonsteroidal inflammatory drugs, the outcome in the majority of cases is favorable.

Poison Control Center data allows for the evaluation of the rate of fatal exposures to OTC analgesic ingredients based on a rough estimate of the total drug exposure. In 1983, the American Association of Poison Control Centers developed the Toxic Exposure Surveillance System (TESS), the only comprehensive poisoning surveillance database in the United States. TESS contains detailed toxicological information on more than 24 million poison exposures reported to U.S. poison centers (AAPCC, 2001), and is a valuable resource for reviewing ingredient safety. Due to various factors influencing

adverse event reporting, the data, however, attribution to a specific agent is often uncertain. For example, fatalities reported under a given drug or drug category might actually be associated with multiple drugs. While the number of adverse toxic events is very low for OTC analgesics considering the widespread usage, Table 18 depicts the number and rate of fatal exposures to aspirin and acetaminophen from 1995 to 2000, inclusive.

In the table below, the number of dosage units sold is used as an estimate of drug exposure and the rate is calculated based on the number of fatalities per 1 billion tablets sold. During this time period the sales for acetaminophen were greater than aspirin. However, it is evident that acetaminophen is associated with both a greater absolute number of fatal events and a higher rate of fatal events.

Table 18. Fatal Exposures (1995-2000)

Year	Acetaminophen		Aspirin	
	Number	**Rate***	**Number**	**Rate***
1995	76	5.47	44	3.03
1996	81	4.31	29	2.03
1997	98	5.16	40	2.8
1998	121	4.03	29	2.1
1999	141	4.48	43	3.07
2000	155	5.18	42	3.18
1995-2000	**672**	**4.7**	**227**	**2.7**

* number of events per 1 billion tablets sold

To account for the differing number of tablets sold between acetaminophen and aspirin subsequently affecting the rate of drug exposure, the rate has been calculated based on the number of fatalities per 1 billion tablets sold. With this adjustment, it is evident that acetaminophen is associated with a greater rate of fatal drug exposure.

8.5.5 Potential Drug-Drug Interactions

Important drug-drug interactions have been reported for both acetaminophen and aspirin that are worthy of mention in product labeling.

Study results suggest a potential interaction between aspirin and commonly prescribed arthritis therapies. In particular, concomitant administration of ibuprofen, but not rofecoxib, acetaminophen, or diclofenec, was found to antagonize the irreversible platelet inhibition by aspirin (Catella-Lawson, 2001). Based on this action, treatment with

ibuprofen in patients with increased cardiovascular risk may limit the cardioprotective effects of aspirin (Catella-Lawson, 2001). The differential effects of ibuprofen, acetaminophen, rofecoxib and diclofenec are likely due to difference in the mechanism of each ingredient. Rofecoxib and diclofenec, which have greater selectivity for the COX-2 enzyme over the COX-2 enzyme, did not interfere with cardioprotective effects of aspirin. Acetaminophen, which is not highly selective for the COX-1 enzyme, did not appear to interfere with aspirin's mechanisms either. However, ibuprofen, which has a greater affinity for the COX-1 enzyme, did interfere with aspirin's mechanistic pathways. The results of this study warrant further analysis and suggest that naproxen sodium and ketoprofen, which have greater selectivity for the COX-1 enzyme than ibuprofen, may also blunt the cardioprotective effects of aspirin. Further study is also warranted to evaluate whether high doses of acetaminophen or multiple dosing regimens might also be detrimental to ibuprofen and therefore should be avoided in users of low dose aspirin for cardiovascular protection.

While NSAID use may interfere with the cardioprotective effects of aspirin, concomitant use of aspirin or acetaminophen with other NSAIDs may also increase the risk of adverse events. The potential interaction of the NSAIDs and the potential increased risk for GI and renal adverse events of these agents warrants cautious use of concomitant aspirin, ibuprofen, naproxen sodium or ketoprofen use with each other or prescription NSAIDs. Similarly, patients utilizing OTC analgesics should avoid repeated doses of products containing other salicylates, including the anti-diarrheal Pepto Bismol® (McEvoy, 2000).

Aspirin is generally contraindicated with oral anticoagulants and heparin (McEvoy, 2000), due to the risk of GI bleeding. However, the American College of Cardiology and the American Heart Association promote the use of aspirin and heparin for management of patients with acute coronary syndrome (unstable angina) (Ryan, 1999). Due to the suspected risk of bleeding associated with aspirin use, acetaminophen has been preferred over aspirin for occasional self-medication in patients on warfarin. However, a recent report involving retroperitoneal hematoma suggests that acetaminophen may interact with warfarin to increase anticoagulation (Andrews, 2002).

Frequent doses of aspirin or acetaminophen should be avoided in patients receiving sulfinpyrazone (Handbook of Adverse Drug Interactions, 2000; McEvoy, 2000). Occasional doses of aspirin for analgesia or antipyresis, however, appear not to decrease the effects of sulfinpyrazone. Likewise, taking one aspirin a day to reduce the risk of a heart attack is usually acceptable. The combination of sulfinpyrazone and acetaminophen, however, is not warranted due to the potential for additive hepatic toxicity (Handbook of Adverse Drug Interactions, 2000).

Combination therapy of corticosteroids and aspirin or NSAIDs may increase the risk of GI toxicity, a known adverse reaction to aspirin and other NSAIDs (Gabriel, 1991; Nielsen, 2001). In light of the potential risk of GI events with acetaminophen use (Garcia-Rodriguez, 2001), further data is needed to fully assess the safety of acetaminophen use with corticosteroids (Fries, submitted, 2002).

Due to the potential seriousness of the interaction, aspirin is contraindicated in patients receiving high dose methotrexate therapy for cancer. Low dose methotrexate therapy for treatment of rheumatic conditions, however, can be used safely with aspirin.

High doses of acetaminophen in combination with anticonvulsants that induce hepatic microsomal enzymes (e.g., phenytoin, barbiturates, carbamazepine) may increase acetaminophen hepatotoxicity (Furey, 1992). However, occasional acetaminophen use is not likely to increase risk of adverse events (McEvoy, 2000). Aspirin, which may displace anticonvulsants from their binding sites, the clinical significance of which is unknown, has minimal adverse effect at OTC doses and therefore does not represent a specific safety concern. Aspirin use with valproic acid, however, requires caution when administered concomitantly, as aspirin can affect the serum concentration, free and total elimination half-life, and metabolism of valproic acid, resulting in adverse reactions.

Aspirin may affect the protein binding of sulfonylureas, a class of drug often prescribed to diabetics. Patients receiving both aspirin and a sulfonylurea may need to have the anti-diabetic drug titrated during and after cessation of aspirin therapy to maintain adequate glucose control (McEvoy, 2000). Also under physician guidance, aspirin may be used in conjunction with other, newer antidiabetic drugs that follow a different mechanistic pathway than the sulfonylureas. Despite potential interactions between some anti-diabetic drugs and aspirin, the American Diabetes Association (ADA) advocates the benefits of aspirin, particularly for use as a primary prevention strategy in men and women with diabetes who are at high risk for cardiovascular events. The ADA position is that while regular use of NSAIDs may increase the risk for chronic renal disease or impair blood pressure control in hypertensive patients, a low dose of aspirin is a very weak inhibitor of renal prostaglandin synthesis and therefore does not have a clinically significant effect on renal function or on blood pressure control (American Diabetes Association, 2002).

Patients taking isoniazid, with acetaminophen are at increased risk of hepatotoxicity (Furey, 1992).

8.5.6 Overdose Potential

Aspirin and acetaminophen are widely available OTC in single-ingredient or combination products for self-medication for treatment of a variety of conditions. Despite the wide availability of products containing analgesic ingredients, the overall incidence of adverse events with proper, OTC use is low, particularly when considering the enormous volume of drug use (Prescott, 2000). However, concern has been raised over multiple product use and corresponding exposure to excessive analgesic levels.

With a variety of OTC products available, there are several conditions under which consumers could be exposed to excessive doses of ingredients. For example, inappropriate dosing could be either intentional (suicide) or unintentional (accidental). The term "therapeutic misadventure" describes conditions in which consumers utilize multiple products simultaneously while being unaware of the possibility of being exposed

to multiple doses of the same ingredient. As outlined in Table 20, the FDA recognizes several possible scenarios through which toxicity may occur.

Table 19: Potential Causes of Toxicity

Potential Cause of Toxicity	Possible Reasons for Occurrence
Use of OTC combination product containing *[ingredient]* with single *[ingredient]* formulation	• Consumers did not know the combination contained [ingredient] (therapeutic misadventure) • Consumer did not understand the possible adverse effects associated with overdosing
Use of Prescription product containing *[ingredient]* with single *[ingredient]* formulation	• Consumers did not know the combination contained [ingredient] (e.g. not adequately labeled by the pharmacy) • Consumer did not understand the possible adverse effects associated with overdosing
Consumer ingested dose amounts that exceeded recommended dosing	• Consumers did not get the benefit with recommended dose so they took more • Consumer was confused by dosing instructions • Consumer believes that because it is OTC it is all right to take more than directed • Consumer gave adult dose to a child not understanding the potential toxicity • Doctor recommended dosing for child without knowing a more concentrated formulation was being used • Intentional overdose
Consumer ingested dose inappropriately	• Consumer took drug despite alcohol abuse • Consumer took dose despite pre-existing contraindicated conditions • Consumer took drug too soon after previous dose • Consumer took drug in combination with other drug presenting interactions

Potential Cause of Toxicity	Possible Reasons for Occurrence
Consumer followed labeled instructions but developed toxicity anyway	• Consumers has known risk factors that may predispose them to the toxicity • There are unidentified risk factors that predispose individuals to toxicity (e.g. other drug, underlying conditions) • The maximum recommended daily dose is too high, or the duration of use is too long

While excessive dosing may occur due to a variety of factors, the toxic potential and severity of overdose outcome varies by analgesic ingredients. The risk of therapeutic misadventure or concurrent use of multiple products resulting in overdose of a single ingredient is most noteworthy for acetaminophen, as the number of products available that contain acetaminophen far outnumber the number of aspirin-containing products (as outlined in Table 21).

Table 20: Products Containing OTC Analgesic Ingredients*

Indication	Acetaminophen	Aspirin
General Analgesic/Antipyretic: Headache, Pain and Fever or Cold, Muscle Aches and Pains, Menstrual Pain, Toothache Pain	98	33
Cold, Flu & Cough	27	0
Allergy, Sinus & Cold	45	2
Heartburn	2	4
Arthritis	1	4
Pain with sleeplessness	17	0
Cardiovascular/Heart Attack	0	5
Total	**190**	**48**

*Count of products is based on currently marketed products detailed in Facts and Comparisons (2000).

As a result of the multitude of products containing acetaminophen, confusion over dosing and co-administration of such products is of great significance, particularly considering the risk of serious hepatic outcome associated with overdose and the prevalence of such serious effects. Acetaminophen accounts for a large percentage of patients presenting to emergency rooms with serious effects, including acute liver failure (Schiodt, 1999). In the United Kingdom, acetaminophen toxicity constitutes the greatest number of emergency inquiries to the UK National Poisons Information Service for any single

agent, and represents 48% of poisoning hospital admissions (Jones 1999). Likewise, acetaminophen use was indicated in 38% of all liver failure cases reported between January 1998 and October 2000 in the United States (Lee, 2001).

8.5.6.1 Clinical Symptoms of Overdose

Symptoms of acetaminophen toxicity, including nausea, vomiting, diaphoresis and general malaise, present within the first 24-48 hours following an overdose. Clinical and laboratory evidence of overdose may not be apparent until 48-72 hours post-ingestion. Acetaminophen overdose, which has been noted with doses over 6 g, and up to 18 g, induces toxic effects primarily on the liver, and can be successfully treated with an antidote, N-acetylcysteine. However, the antidote treatment is most effective immediately following overdose. Due to the unnoticeable early signs of overdose and time sensitivity for administration of the antidote, acetaminophen overdose often results in injury more serious than reversible effects of other OTC analgesic overdose.

Unlike acetaminophen, aspirin overdose syndrome, which has been noted at doses greater than 6 to 10 g in adults (serum salicylate concentrations >300 μg/mL) or in excess of 150 to 200 mg/kg of body weight, is generally recognized within 3 to 4 hours after overdose. Signs of overdose include nausea, vomiting, tinnitus, hyperthermia, and hyperventilation. Respiratory alkalosis, metabolic acidosis, hypoglycemia, dehydration, visual disturbances, hallucinations, seizures, and delirium can occur at later stages. With prompt recognition of the symptoms of overdose, the clinical effects of aspirin overdose are usually reversible through supportive and palliative care.

8.5.6.2 Children and Overdose

Acetaminophen overdose is of particular relevance in children, as acetaminophen is the favored OTC ingredient in this population. Like many drugs, the usual dose of acetaminophen is based on body size, with much lower dose recommend for children than for adults (160-480 mg/dose for children ages 2-12 versus 500-1000 mg/dose for adults). Despite dosing recommendations, a study of reported cases of acetaminophen hepatotoxicity in children found that 52% of the children received adult preparations of acetaminophen (Heubi, 1998). Fifty-five percent of the children reported in these cases died of hepatic failure, and 3 patients survived only after liver transplantation. Based on the differences in dosage requirements, the narrow therapeutic index, and additive effects of acetaminophen from various co-administered products, the American Pediatrics Academy warns that children are at greater high risk for acetaminophen overdose (American Pediatrics Academy, 2001). This risk is exacerbated by the lack of awareness of the potential toxicity due to overdose, and that there are multiple children's products, which contain acetaminophen, that may lead to therapeutic misadventure.

Because aspirin is not widely used in children, there is lower risk of potential overdose in children as compared to acetaminophen.

8.5.6.3 *Intentional Overdose*

Because of its toxic potential, acetaminophen is one of the most frequently used drugs in intentional overdose (Gunnell, 2000). A population-based retrospective study (Bond 1999) in the US observed that the incidence of hospitalization for acute acetaminophen toxicity was 4.8/100,000/year (95% CI= 3.0-6.5) and for acute and chronic acetaminophen poisoning was 5.5/100,000/year (95% CI= 4.1-7.0). Most of the patients (89%) in this study took a single, greater than therapeutic dose of the drug and that concomitant alcohol consumption was a predictor of hepatic failure. As such, the investigators advocate the use of package-size limitations as a means of reducing the incidence of acetaminophen toxicity and overdose (Gunnell, 2000).

National policies regarding acetaminophen package-size limitations have been implemented in some countries. While some data suggest that package size limitations may affect suicidal behavior and the incidence of hepatotoxicity, (Hawton, 2001), recent data suggest that reduced acetaminophen availability may not impact the incidence of severe liver failure due to acetaminophen use (Robinson, 2000). Data also suggest that package restrictions on acetaminophen may lead to an increased poisoning with alternative analgesics (Balit, 2002). Additionally, while package size limitations may potentially affect the incidence of overdose with acetaminophen, it is unlikely that similar restrictions on aspirin or NSAID packaging would affect the rate of NSAID or aspirin mortality, as overdose with aspirin or NSAIDs results in vomiting and other symptoms that encourage consumers to seek medical attention. Furthermore, the inconvenience caused by package limitations may adversely affect consumers of aspirin who require daily aspirin for cardiovascular prevention.

8.6 Benefits of Product Specific Labeling

The Food and Drug Administration (FDA) has the responsibility to assure proper labeling of OTC drugs and to protect against the distribution of labeling that is false or misleading, or that fails to provide adequate directions for use. Furthermore, FDA requires clear, concise labeling on OTC drugs that communicates important product information to the consumer, as found on the Drug Facts Label.

The importance of clear and precise labeling is highlighted by the fact that product labels are often the only method of conveying safe and proper self-medication guidance to consumers seeking symptom relief without a doctor's oversight. The FDA has recently announced the requirement for all non-prescription drugs to carry clear, simple and readable ("Drug Fact") labeling to make it easier for consumers to understand information about the products, benefits and risks, and how the drugs should be used most effectively (FDA, 1998). A specific, comprehensive label enables consumers to choose the right product to meet their symptoms and personal health needs. The more detailed a label is to a specific drug, the more informative it will be.

The realized benefits of clear, concise informative labeling will depend on the degree to which consumers are able to act on information to make choices that could reduce drug side effects, drug interactions, allergic reactions, and other unintended consequences of self-medicating. As such, concise and actionable warnings are warranted, and approaches that tend to minimize the effectiveness of a warning to ensure class consistency should be avoided.

8.6.1 Informative Warning Labels

The warning section of a product label contains information that is relevant to both the selection of the appropriate product and for proper use. According to the FDA, this section should contain information regarding when the product should absolutely not be used, drug-drug and drug-food interactions, possible side effects, when a consumer should consult a doctor or pharmacist *before* taking the product, and when to stop use and contact a doctor *after* taking the product (FDA, 1998). This information can be conveyed through two types of product warnings, which are enforced by the FDA: ingredient-specific warnings and broad-class labels.

8.6.1.1 Ingredient-Specific Warnings

The Reye syndrome-warning label, which is required by the FDA on all salicylate-containing products, represents a positive example of ingredient-specific labeling. Several case reports raised concern regarding a possible link between aspirin use in children, particularly those with flu-like symptoms or any other viral illnesses, including chicken pox (Desjardins, 1998), and the development of Reye's syndrome. After the instatement of the warning on aspirin products in 1986, there was a dramatic reduction in

the occurrence of Reye's syndrome in the United States (Committee on Infectious Disease, 1982; Belay, 1999). According to the Centers for Disease Control and Prevention, 555 cases of Reye's syndrome were reported among American children in 1980; where as no more than 36 cases have been reported per year since 1987 (Belay, 1999). It is widely held that the powerful ingredient-specific warning, along with a public education campaign, resulted in the dramatic decrease in incidence (Monto, 1999).

Based on the effectiveness of the Reye's syndrome label, it can be assumed that ingredient-specific labeling empowers the consumer to make wise self-medication decisions. As such, ingredient-specific labeling should be considered for optimizing the safe use of OTC products containing active ingredients that may be associated with adverse events.

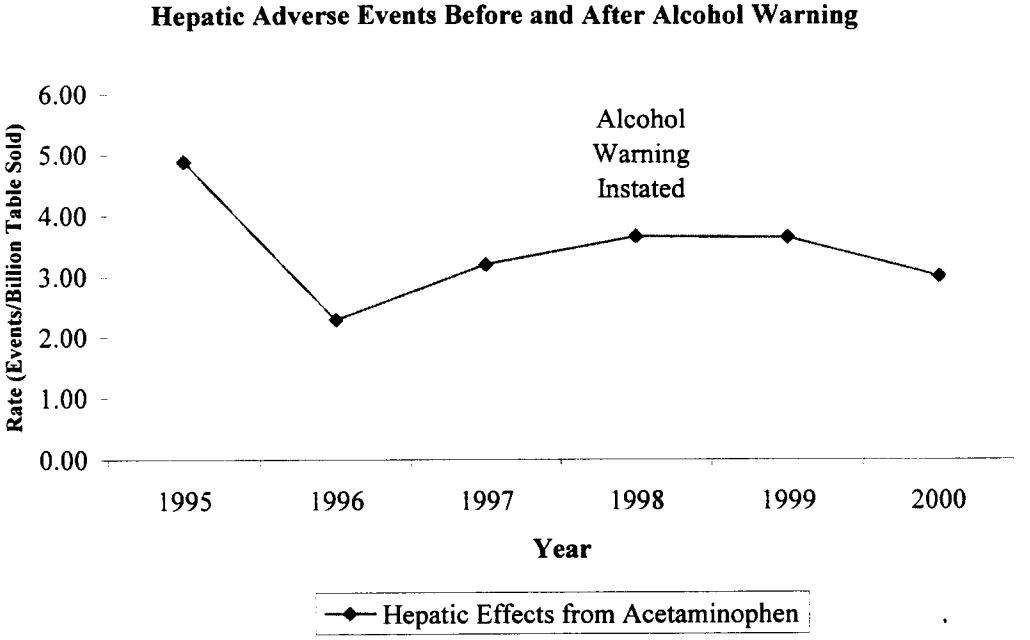
8.6.1.2 Broad Class Warnings

If drugs were all labeled according to broad class regulations, ingredient- specific drug interactions, contraindications and adverse events would not be explicit, thus leading to possible consumer confusion. Additionally, broad class labeling of drugs may suggest to consumers that all the drugs in the class are equivalent, and may be used interchangeably. This erroneous assumption may cause patients to misunderstand or confuse important ingredient-specific dosing information, leading to unwarranted adverse events.

The alcohol warning on OTC analgesics is an example of a broad class label. Data supporting the relationship between alcohol and acetaminophen hepatotoxicity prompted the FDA to establish a final rule in 1998 requiring all non-prescription analgesic products to have a label warning consumers of the interaction of alcohol and OTC analgesic products (FDA, 1998). While this alcohol warning highlights the potential adverse reaction interaction, it likely falls short in warning consumers of the unique risk of hepatic injury with acetaminophen use by blanketing all OTC analgesic products.

The incidence of specific adverse events of relevance to aspirin and acetaminophen can be compared prior to and following the instatement of the alcohol warning in 1998. As shown by data from the WHO adverse event database, the incidence of adverse events specific to acetaminophen and aspirin did not change significantly as a result of the alcohol warning (Figure 2).

Figure 2: Average Rate of Hepatic Adverse Events Reported per 1 Billion Tablets Sold Before* and After† the Alcohol Warning on Acetaminophen



8.6.1.3 Influencing Consumer Decisions

Comprehensive, credible information allows physicians, patients and consumers to make informed health care choices that will maximize benefit and reduce risk. Surveys suggest that labeling is a key factor in consumers' purchase decisions. In fact, 80% of consumers use OTC labeling for information about these products more so than they use doctors (75%) or pharmacists (70%) (American Pharmaceutical Association, 1997). Likewise, the vast majority of consumers (79%) always read the label when purchasing an OTC product of the first time (American Pharmaceutical Association, 1997).

Based on the large percentage of the population that reads label directions to aid purchase decisions, the FDA has developed a consumer-oriented label that will optimize consumer comprehension and aid in safe product use. The FDA contends that clear, concise labeling that clearly identifies a product, its ingredients, uses, warnings and directions will provide at least three important benefits: (1) enhance the therapeutic value of OTC drug products by helping consumers select appropriate products and adhere to proper dosage regimens; (2) allow consumers to avoid ingredients or products that in some circumstances cause adverse events such as allergic reactions, adverse drug interactions,

or other unintended outcomes, ranging from minor discomfort to hospitalization; and (3) allow consumers to quickly identify key elements of product information, such as appropriate ingredients, uses, and warnings, thereby increasing the economic efficiency of their OTC drug purchases (FDA, 1999).

The FDA realizes that consumers most need to know what the product is and what it is intended to do. Accordingly, the FDA requires that the product brand name (e.g. Tylenol®; Bayer Aspirin®) and pharmacologic activity (e.g. pain reliever) be displayed on the front panel of the product. Likewise, the FDA requires the identification of active ingredient(s) (e.g. acetaminophen; acetylsalicylic acid). The agency strongly believes that consumers need to be able to identify the active drug ingredients, and should be able to readily access that information, as consumers associate ingredients with their respective purposes. Research suggests that consumers use ingredient-specific information, with brand-name associations and knowledge of pharmacologic activity, to aid in product selection and self-medication regimens. Consumers associate brand names with product attributes that position the product in the market and distinguish competing products from each other (FDA, 1997), and consumers use the pharmacological activity of a product to understand the correct uses for a product. In knowing the specific active ingredients of a product, consumers are able to make active judgments on the basis of product's chemical contents (FDA, 1997).

Single-ingredient products are required to state the brand name, pharmacologic properties and active ingredients on the principle display panel of the product, thus allowing consumers to quickly and easily understand what is in a particular product. Combination products, however, are required to list only the brand name and statement of pharmacologic activity on the front of the packaging. For combination products, the FDA requires that active ingredients and their purposes be prominently presented under the title "Drug Facts." While active ingredients are listed on the back of product packaging, consumers may not always associate specific ingredients with combination products, potentially increasing the risk of ingredient overdose due to multiple product use.

In addition to product name, ingredients and pharmacologic activity, other important dosing and product use information is important in helping consumers make selection decisions and use products safely. Because consumers need to select an appropriate product for its intended uses, the FDA requires, product "Use(s)," and "Warning" sections to be placed following the active ingredient and purpose information. After a consumer selects an appropriate product, correct administration and dosing is essential to ensure safe use. Thus, the FDA mandates that the "Directions" section contain dosage and administration information necessary for the safe and effective use of the product.

8.6.2 Reducing Adverse Events

Studies of the number of events attributable to the unintended consequences of OTC drug therapy, excluding admissions due to overdose, intentional poisoning, attempted suicides,

drug abuse or intoxication, suggest that the percentage of hospitalizations due to adverse drug reactions range from between 4 (Ives, 1987) and 18 percent (Caranasos, 1974; Mitchell, 1988). The FDA estimates that unintended OTC drug-related hospitalizations may account for about 0.55 percent (5.5 percent x 10 percent), or 170,500 of the nation's 31 million annual hospital admissions (FDA, 1999). Investigators have determined that between 48 and 55 percent of all hospital admissions related to adverse reactions are preventable (FDA, 1995). Thus, product labeling should be enhanced through ingredient-specific warnings to increase safe drug use.

8.6.3 Reducing Economic Costs

Due to the economic impact of serious adverse drug reactions, measures to ensure safe product use are of utmost importance. Based on the assumption that 50 percent of the hospitalizations attributable to OTC drug adverse reactions are preventable (FDA, 1995) and that the cost of an average hospital stay is $9,191 (Agency for Health Care Policy and Research, 1995), the FDA finds that $784 million is spent annually on hospitalizations due to potentially avoidable OTC drug adverse drug reactions.

In addition to reducing the costs of healthcare, the indirect benefits from reduced drug-related illnesses due to enhanced product labeling include avoiding costs incurred with lost work time or reduced productivity. The FDA roughly estimates that the value of lost productivity is $44.2 million patients for aged 20 to 60 and $8 million for the remaining patients or their care-givers (U.S. Department of Commerce, 1998).

8.6.4 Labeling Recommendations

Based on the widespread use of OTC analgesics for treating mild to moderate pain, it is evident that consumers seek the benefits of the variety of products currently available. Non-specific restrictions on use and dosing of specific ingredients, which could restrict consumer use of certain products, may inaccurately suggest to consumers that analgesic products are not unique preparations. Clear labeling, on the other hand, presented in simple language that identifies contraindications for specific agents and instructions for effective use educates and empowers the consumer to make enlightened choices.

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