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Dockets Management Branch (HFA -305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

**RE: Docket 77N-0941**

**Response to Proposed Rule of August 21, 2002 to amend the Tentative Final Monograph for Internal Analgesic, Antipyretic and Antirheumatic Drug Products for OTC Use to include ibuprofen as a generally recognized safe and effective analgesic/antipyretic active ingredient for OTC use.**

Dear Sir/Madam:

Wyeth Consumer Healthcare submits the attached comments in response to the above referenced notice published by FDA on August 21, 2002.

If you have comments or questions, please contact the undersigned at 973 660-5753 or Ms. Mary Davis at 973 660-5825.

Sincerely,  
WYETH CONSUMER HEALTHCARE

A handwritten signature in black ink that reads "Sharon Heddish".

Sharon C. Heddish  
Vice-President, Regulatory Affairs

77N-0941

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## Table of Contents



**TABLE OF CONTENTS**  
**Ibuprofen Monograph Response**

<b>COVER LETTER</b>	-----
<b>MONOGRAPH RESPONSE</b>	Vol. 1 , pg. 3
<b>APPENDIX I</b>	Vol. 1 , pg. 33
<b>APPENDIX II</b>	Vol. 1 , pg. 78
<b>APPENDIX III</b>	Vol. 1 , pg. 228



## **I. INTRODUCTION**

On November 25, 1997, Wyeth Consumer Healthcare (formerly Whitehall-Robins Healthcare) submitted a Citizen's Petition requesting that ibuprofen, in a 200 mg oral dosage form, up to 1200 mg per day, be generally recognized as safe and effective for over-the-counter (OTC) use. Accordingly, the petition requested that the Agency amend the Tentative Final Monograph (TFM) for Internal Analgesic, Antipyretic, and Antirheumatic (IAAA) drug products for OTC human use to include oral ibuprofen.

On August 21, 2002, the Food and Drug Administration published a proposed rule to amend the TFM to include oral ibuprofen 200 mg tablets as a generally recognized safe and effective analgesic/antipyretic for OTC use. However, as part of the proposed rule, a significant number of new label warnings were suggested by the Agency. In addition, the risks of GI and renal toxicity associated with OTC analgesics were discussed at a joint meeting held between the FDA and the Nonprescription Drug Advisory Committee (NDAC) on September 20, 2002. At that meeting, NDAC also made recommendations regarding warnings for ibuprofen (as well as other OTC NSAIDs). The Agency has indicated that NDAC's recommendations may be included as comments to the proposed rulemaking.

This document presents Wyeth Consumer Healthcare's (WCH) comments on the new warnings and other recommendations made by the Agency and/or NDAC.

## **II. SAFETY OF OTC IBUPROFEN**

The Agency based its recommendation to include ibuprofen in the TFM, in part, on the very favorable safety profile that OTC ibuprofen has exhibited since it first became available to consumers in 1984.

As presented in a background document that WCH provided to NDAC (Appendix I), there is overwhelming data derived from numerous sources, including controlled clinical trials, epidemiology studies, as well as safety surveillance data, supporting the excellent safety profile of OTC ibuprofen. These data clearly demonstrate that:

- Not all NSAIDs have the same safety profile;

- For any NSAID, the risk of developing serious events is related to dose and duration of use;
- Ibuprofen consistently exhibits the most favorable GI safety profile of all NSAIDs;
- The approved OTC daily dose of ibuprofen (1200 mg/day) is 37.5% of the maximum daily prescription dose (3200 mg); when OTC doses of ibuprofen (200-400 mg/dose; 1200 mg/day) are taken for acute episodes of pain (i.e., up to 10 days), its GI safety profile is even more favorable than at prescription doses, with an extremely low risk of causing serious gastrointestinal events;

A meta-analysis of epidemiology studies has shown that when administered at low prescription daily doses of 1500 - 1800 mg, ibuprofen has a relative risk of GI adverse events that is not significantly different from that of the general population (RR=1.42, 95% CI 0.93, 2.15)<sup>1</sup>;

A case-cohort study specifically designed to estimate the relative risk of GI bleeding associated with OTC doses of naproxen sodium and ibuprofen evaluated events which occurred within the first 2 weeks of dosing among those Medicaid patients whose average daily dose was  $\leq$  600 mg/day of naproxen sodium or  $\leq$  1200 mg/day of ibuprofen. The analysis indicated that the incidence of GI bleeding associated with both drugs was extremely low (0.012% for ibuprofen and 0.026% for naproxen sodium)<sup>2</sup>;

Despite very extensive use, over the 18 years that ibuprofen has been available OTC, the Agency has received an average of approximately 18 reports per year of GI perforations, ulcers or hemorrhage associated with OTC ibuprofen;

- The frequency of renal side effects with OTC ibuprofen has also been shown to be low (less than 2 cases of renal failure per year), further confirming that nonprescription ibuprofen is well tolerated;
- Eighteen years of post-marketing safety surveillance has identified no new, significant health risks to the population associated with the use of OTC ibuprofen.

WCH believes that this long history of safe and effective use of OTC ibuprofen indicates that the current OTC label has been effective in communicating the appropriate use of the product.

### **III. CONSUMER COMPREHENSION OF CURRENT LABEL**

The current label for OTC ibuprofen instructs consumers to use the minimal effective dose. Specifically, the directions recommend initiating treatment with one 200 mg tablet, increasing to two (400 mg), if needed. Other dosing instructions state:

- Do not take more than directed
- Use the smallest effective dose

In addition, consumers are directed to ask a doctor before use if they have had problems or side effects with any pain reliever/fever reducer or if they have had stomach pain. They are also advised to ask a doctor or pharmacist before use if:

- they are under a doctor's care for any continuing medical condition
- are taking other drugs on a regular basis, or
- if they are taking another product containing ibuprofen, or any other pain reliever/fever reducer.

WCH recently conducted a label comprehension study of the current label, which included elderly individuals as well as those with low literacy. The survey revealed that the communication goals of the label are very successfully met. Specifically, the survey showed that:

- Dosage instructions were well understood: 98% correctly stated the initial recommended dosage, 89% correctly indicated the maximum number of tablets per dose, and 92% correctly indicated the maximum daily dose;
- When consumers were presented with scenarios describing situations in which consumers should, or should not use Advil without first consulting a doctor, anywhere from 85% to 99% responded correctly to the 11 scenarios presented to them;
- Two-thirds of current users had consulted with a physician about their use of Advil;
- Understanding of label directions and appropriate usage were equally high among both younger and older (50+) consumers, as well as low and high literacy consumers.

A copy of the final report of the label comprehension study can be found in Appendix II.

That the current OTC label has been effective in communicating the appropriate use of the product is further supported by consumer research and actual-use clinical study data, which show that the vast majority of OTC consumers use the product in conformance with the label instructions.

- Data from a 2002 Gallup survey indicate that consumers of OTC ibuprofen use an average of only 17.1 pills per month; only 6.5% use > 50 pills/month<sup>3</sup>;
- In a 1996 Attitude and Usage study conducted over a 10-day period, the average number of tablets taken per dose was approximately 2, the average number of tablets taken per day was 3.6 (~720 mg); more than 6 tablets per day (>1200 mg) were taken only 8% of the time.<sup>4</sup>

#### **IV. MODIFICATIONS TO THE CURRENT OTC IBUPROFEN LABEL SHOULD BE DATA DRIVEN**

WCH believes that any label modifications intended to better address safety concerns should be based on safety data from ibuprofen and not from data derived from NSAIDs as a class, nor from data on prescription doses of ibuprofen (> 1200 mg/day, for an unlimited period of time). Unfortunately, much of the data presented at the September 20<sup>th</sup> NDAC meeting, as well as that discussed in the Agency's proposed rulemaking, did not make these distinctions.

Specifically, data from several case control studies evaluating the incidence of GI and renal complications associated with NSAID use (based on prescription databases) were presented to NDAC.<sup>5-9</sup> The majority of the data that was presented lumped all NSAIDs together, and for the most part, failed to distinguish dose and duration of use. Accordingly, the following conclusions were presented to the Committee:

- The risks of GI complications from NSAID use are increased with age, corticosteroids, coumadin, and use with other NSAIDs;
- The risks of renal complications from NSAID use are increased with age, diuretics, ACE inhibitors, and other co-morbid conditions.

NDAC was also told (in the absence of any supportive data) that these data were relevant to OTC NSAIDs since: “OTC drugs may be self administered as previously “prescribed” (high dose)” and “OTC drugs may be used for long duration”.

Although data were presented which showed that OTC ibuprofen was not associated with an increased risk of renal toxicity in those > 65 years of age (RR = 0.94),<sup>9</sup> this was not discussed at any length by the committee. Finally, it really wasn't made clear to the Committee that in most cases, the NSAIDs (regardless of dose) were taken on a chronic basis. Accordingly, WCH believes that these data and the ensuing discussion among the Committee members had little relevance to true OTC use of ibuprofen.

Another study discussed in some detail at the NDAC meeting was an analysis of the American College of Gastroenterology (ACG) bleeding registry completed by Blot and McLaughlin.<sup>10</sup> Their survey was of particular interest to the Committee since it was designed to evaluate the potential risks of GI bleeding associated with OTC NSAIDs. The ACG bleeding registry was generated in 1995 by having members of the ACG participate in a mail survey where they were asked to provide information on up to 10 patients with GI bleeding and 10 procedure-matched patients without GI bleeding. The analysis found that of those patients in the registry who developed GI bleeding, 10.1% reported taking OTC doses of ibuprofen, compared to 5.8% of controls. The odds ratios were related to the dose of ibuprofen as follows:  $\leq 600$  mg per day had a ratio of 1.8 (95% CI 0.8, 4.1), while  $\leq 1200$  mg per day had a ratio of 3.5 (95% CI 1.2, 10.7).

These results of this study were first presented at the 1995 meeting of the American College of Gastroenterology. When asked to comment on the findings, the Director of FDA's Office of Drug Evaluation V at the time stated “This study has some serious and important defects....”

WCH has asked two independent experts to provide a critique of this study. A complete copy of their reviews can be found in Appendix III. Some of the significant methodological flaws noted are as follows:

- Information on cases, as well as controls, was provided by the physicians in a non-randomized, non-blinded manner. Physicians were instructed to complete the survey for up to 10 bleeding patients and 10 procedure-matched controls. Although physicians were instructed that the procedure-matched control was to be the next patient (either inpatient or outpatient) having the same procedure as the case subject, there was no way to confirm that the physicians adhered to these instructions. Furthermore, data were presented for 627 cases and only 590 controls, without any explanation of the imbalance (furthermore, the number of cases and controls should have been divisible by 10);
- The non-randomized, non-blinded study design also created an obvious selection bias;
- The controls used for this study were inappropriate and led to bias. Hospitalized controls were subjects much sicker than typically used patients from the same community that cases were chosen. Cases almost were certain to have less exposure to NSAIDs and patients with GI symptoms sick enough to require endoscopy are frequently advised to avoid NSAIDs prior to the procedure;
- Critical information regarding duration of use was not collected, therefore, the relevance of these data to true OTC use of ibuprofen is unknown.

Based on these significant methodological shortcomings, WCH believes it is difficult and inappropriate to draw any conclusions from this study.

V. **COMMENTS ON PROPOSED NEW LABEL WARNING “ASK A DOCTOR BEFORE USE IF YOU HAVE STOMACH PROBLEMS THAT LAST OR COME BACK, SUCH AS HEARTBURN, UPSET STOMACH, OR PAIN”**

Although this proposed warning is already included in the TFM for IAAA drug products, WCH does not believe that there are data to support this warning. There is no correlation between the occurrence of these symptoms and serious clinical outcomes such as GI ulcers or bleeding following NSAID use.<sup>11-15</sup> In fact, in one prospective, cohort study, more than 80% of the patients who developed serious GI complications following NSAID use did not experience any GI symptoms prior to the event.<sup>16</sup>

WCH is also aware of no data to suggest that individuals who frequently experience episodic heartburn or who have gastrointestinal reflux disease are at an increased risk of either exacerbating their symptoms or experiencing more serious clinical outcomes following NSAID use.

Although OTC ibuprofen is perceived by the medical community (perhaps due to their experience with prescription NSAIDs) to cause GI upset and other GI symptoms, two controlled clinical trials conducted by WCH involving over 4400 subjects who received ibuprofen clearly demonstrate that this is not the case. In these trials, the reported rate of GI symptoms (such as abdominal pain, dyspepsia, etc.) when ibuprofen was administered at 1200 mg/day for 10 days was not distinguishable from placebo or celecoxib (evaluated in only one study).<sup>17,18</sup> These studies are described in more detail under Section VI below.

**VI. COMMENTS ON PROPOSED NEW LABEL WARNING “ASK A DOCTOR OR PHARMACIST BEFORE USE IF YOU ARE OVER 65 YEARS OF AGE”**

While the elderly may be at an increased risk of experiencing serious GI and/or renal events when ibuprofen is taken at prescription doses on a chronic basis, based on data from a variety of sources, including controlled clinical trials, epidemiology studies, and safety surveillance data, this subgroup of consumers do not appear to be at an increased risk of an adverse outcome when ibuprofen is administered at OTC doses and for a short duration of use (i.e., up to 10 days). These data are summarized below.

**GI and Renal Safety Data in Those >65 years from Controlled Clinical Studies**

The safety of ibuprofen administered at OTC doses for up to a maximum of 10 days has recently been studied in three prospective, randomized, double-blind clinical trials. While these studies had limited power to detect rare, significant adverse events, they were useful in evaluating the incidence of more frequently occurring, non-serious side effects associated with NSAID use.

- The PAIN study, which was conducted by Moore, et al., was designed to compare the safety of ibuprofen (1200 mg/day), with aspirin (3000 mg/day) and acetaminophen (3000 mg/day) in the treatment of acute pain in 8677 patients for up to seven days.<sup>19</sup> Although

the authors did not indicate the proportion of the population who was over 65 years of age (the mean age of the population was ~44 years), nor present specific data on the elderly, **the authors indicated that the results were consistent when the data was evaluated according to age.** In that trial:

Ibuprofen was associated with a significantly lower rate of GI complaints (4.0%) compared to both aspirin and acetaminophen (7.1% and 5.3%, respectively);

There were no serious GI events with ibuprofen, compared to an incidence rate of 0.14% for aspirin, and 0.1% for acetaminophen;

The rate of discontinuation was low for all three treatments, and lowest for ibuprofen (5.1% versus 7.8% and 6.1% for aspirin and acetaminophen, respectively);

There was not a single report of a serious renal event.

As previously mentioned, WCH has conducted two Multiple Use Safety and Efficacy Studies (MUST I and II), which evaluated the safety of ibuprofen administered at the maximum daily OTC dose (1200 mg/day) and duration for use (10 consecutive days) in subjects representative of the OTC analgesic consumer population.<sup>17,18</sup> MUST I compared the GI safety profile of OTC ibuprofen to placebo in 1246 subjects, of whom 234 were 65 years of age or older. MUST study II compared OTC ibuprofen to celecoxib 200 mg/day, as well as placebo, and enrolled 2249 subjects, of whom 466 were 65 years of age or older. As an indirect measure of blood loss, fecal samples were collected in both studies and analyzed for occult blood. **The results from the subgroup of elderly subjects in these trials were consistent with the overall population.** In this subgroup:

- The incidence of GI symptoms for ibuprofen was no different from placebo in both studies. In addition, the incidence of GI symptoms for celecoxib was similar to that of ibuprofen (MUST II).
- There was one serious GI event in each study; each event occurred in an individual older than 65 years, although in each case, the events were considered unrelated to study medication;

in MUST I, there was one report of GI ulcer, bleeding and diverticulitis with ibuprofen in a man 67 years of age. These events were considered unrelated to ibuprofen because the subject denied taking any study medication;

in MUST II, there was one report of diverticulitis in a 73-year-old subject who had received ibuprofen during the trial. The event was considered unrelated to the drug since it occurred 7 days after the completion of the study;

- In both trials, the incidence of subject withdrawal due to an adverse event in those  $\geq 65$  years was low and consistent with that of the overall population. There were no significant differences between treatment groups;
- In MUST I, there were only 2 subjects (0.9%) who were 65 years or older who had a positive fecal occult blood test, one was in the placebo group, and one in the ibuprofen group (in the overall population, 17 subjects – 1.4% of the population had a positive test); in MUST II, there were four subjects (0.9%) who had a positive test, all of them in the ibuprofen group (in the overall population, 11 subjects – 0.5% had a positive test).
- There were no reports of any renal events in either study.

In addition to these three large scale studies, Bradley et al., conducted a 4-week study evaluating the safety and efficacy of ibuprofen 1200 mg/day, ibuprofen 2400 mg/day and acetaminophen 4000 mg/day in the treatment of osteoarthritis in 184 subjects.<sup>20</sup> Although the authors did not indicate how many of these subjects were  $> 65$  years, the median age of the treatment groups ranged from 55.7 to 57.2 years. While the duration of this trial (4 weeks) was considerably longer than the recommended OTC usage (up to 10 days), the incidence of GI adverse events with ibuprofen 1200 mg/day was similar to acetaminophen 4000 mg/day. There were no reported renal adverse effects with ibuprofen 1200 mg/day, compared to one with acetaminophen. There were also no changes in serum creatinine concentrations over the 4 week study with ibuprofen 1200 mg/day.

Furey, et al. evaluated renal function in eight elderly patients following the administration of ibuprofen 1200 mg/day for seven days.<sup>21</sup> **The study showed that OTC ibuprofen had no**

**effect on renal function in these older individuals. No serious GI events were reported in the study.**

Taken together, these studies show that the GI and renal tolerability of low-dose, short-term ibuprofen use in the elderly is very favorable, and comparable to that observed in the overall population. Although these trials had limited power to evaluate the incidence of serious events because of their sample sizes, they do provide supportive data that the incidence of serious GI and renal events with OTC ibuprofen is very rare in the elderly.

### **Epidemiology Studies - GI**

At the September 20<sup>th</sup> NDAC meeting, data from a recently published meta-analysis of three previously published epidemiology studies involving elderly patients were presented by Dr. Michael Langman. The demographic characteristics of these populations are presented in Table 1.

**Table 1. Demographic Characteristics of the Three Studies included in Meta-Analysis by Lewis et al.<sup>22</sup>**

Parameter	Study		
	British <sup>23</sup>	Catalan <sup>24</sup>	Swedish <sup>25</sup>
# Cases/Controls	1131/2114	875/2626	466/1137
Age (Mean ± SD)	74 ± 7.8	58 ± 17.1	64 ± 15.2
% Male/Female	56/44	69/31	53/47
% Hx UGI Problems	40	36	0

<sup>22</sup> Lewis, et al. Br J Clin Pharmacol 2002;54:320-326.

<sup>23</sup> Langman, et al. Clin Pharmacol Ther 1993;53:485-594.

<sup>24</sup> Laporte, et al. Lancet 1991;337:85-89

<sup>25</sup> Kaufman et al. Clin Pharmacol Ther 1993;53:485-494.

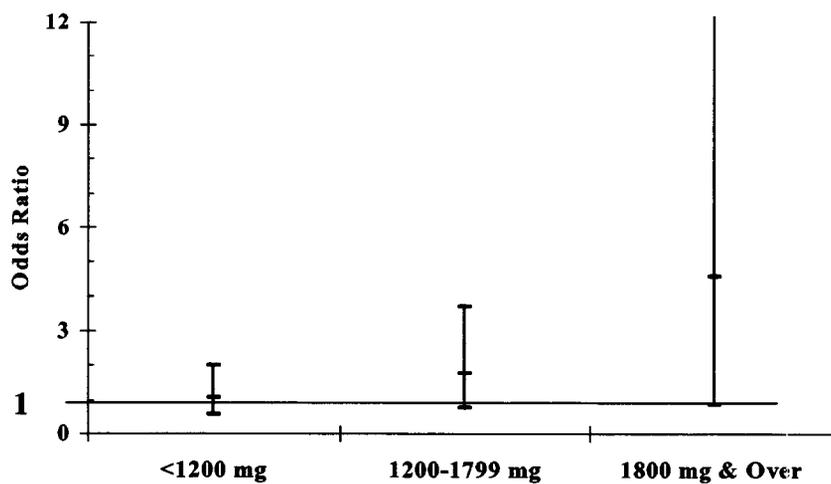
Key results from the study are presented in Figure 1.

- The pooled relative risk of developing a serious GI event for ibuprofen (regardless of dose) in these studies was 1.7 (95% CI = 1.1-2.5); the pooled relative risk of developing a serious GI event for acetaminophen was 1.2 (95% CI = 1.1-1.5);

- At doses < 1200 mg, the relative risk of developing a serious GI event for ibuprofen was 1.1 (95% CI = 0.6-1.2);
- The risk of developing a serious GI event with ibuprofen increased with increasing doses: at doses 1200 mg to 1799 mg, the relative risk was 1.8 (95% CI = 0.8-3.7); at doses  $\geq$  1800 mg, the relative risk was 4.6 (95% CI = 0.9 – 22.3).

**Figure 1**

**Odds Ratios (95% C.I.) of Upper GI Bleeding  
According to Ibuprofen Dose**



Data from Lewis, et al.

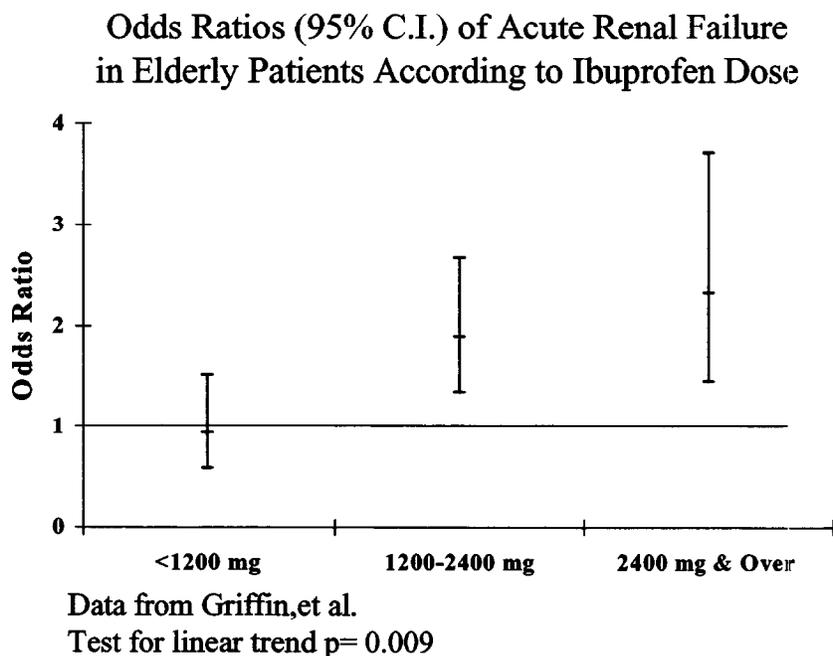
Note: Upper Confidence limit exceeding 12 is truncated

These data are remarkably consistent with data generated from a meta-analysis of 16 studies involving all age ranges (including the three trials discussed above).<sup>1</sup> That analysis, completed by Henry et al., showed that at daily doses of 1500–1800 mg, ibuprofen has a relative risk of GI adverse events that is not significantly different from that of the general population (RR=1.42, 95% CI 0.93, 2.15). **The consistency of the findings support the conclusion that the elderly are not at an increased risk of developing serious GI events with OTC ibuprofen.**

### **Epidemiology Studies - Renal**

As was also presented at the September 20<sup>th</sup> NDAC meeting, Griffin et al., reviewed the records of 1,799 patients  $\geq 65$  years old enrolled in the Tennessee Medicaid program from 1987 – 1991 who had acute renal failure.<sup>9</sup> Of the 1,799 patients, 18.1% were current users of NSAIDs. Ibuprofen accounted for 35% of the NSAID users. There was found to be no associated risk of acute renal failure in those who took ibuprofen  $\leq 1200$  mg/day (RR=0.94, 95% CI 0.58, 1.51). Risk was found to increase according to dose, as shown in the following figure.

**Figure 2**



A study by Rexrode, et al. examined whether analgesic use is associated with an increased risk of renal dysfunction.<sup>26</sup> This cohort study included 11,032 previously healthy men (of whom 2545 were  $\geq 60$  years of age) who provided blood samples and a self-report of analgesic consumption. The main outcomes measured during this 14-year study of men 40-84 years were elevated creatinine levels ( $\geq 1.5$  mg/dL), a reduced creatinine clearance ( $\leq 55$  mL/min), versus self-reported use of acetaminophen, aspirin, and NSAIDs (never [ $<12$  pills], 12-1499 pills, 1500-2499 pills, and  $\geq 2500$  pills). Mean creatinine levels and

clearance were similar between the groups that used analgesics and those who did not, even where use exceeded 2500 pills. Multivariate analysis (adjusted for age, body mass, history of hypertension, elevated cholesterol, diabetes, cardiovascular disease, physical activity, use of other analgesics) indicated that the relative risks of elevated creatinine levels associated with intake of  $\geq 2500$  pills were 0.83 (95% C.I. 0.50-1.39) for acetaminophen, 0.98 (95% C.I. 0.53-1.81) for aspirin, and 1.07 (95% C.I. 0.71-1.64) for other NSAIDs. No association was observed between analgesic use and reduced creatinine clearance. **Although specific data were not presented, the authors indicated that they found no increased risk among those who were 60 years of age or older.** These data indicate that the moderate use of analgesics in a cohort of initially healthy men was not associated with increased risk of renal dysfunction, even in the elderly.

#### **Safety Surveillance Data**

Data from FDA's spontaneous reporting system for all single-ingredient ibuprofen products from the period of July 1996 through March 2002 (subsequent to the submission of the monograph petition) have been reviewed by WCH. These data included only the reports of adverse events associated with the administration of ibuprofen for ten days or less, at doses of 1200 mg/day or less, and in subjects 12 years of age or older, with no reported use of concomitant drugs. Over this approximately 6-year period, a total of 41 serious reports including at least one GI system term were reported. The mean age of the 39 patients whose age was provided was 52.4 years (range = 14 – 95 years), and 14 of the 39 patients (36%) were older than 65 years. Of the serious GI reports, 20 (50%) were related to perforation, ulcers and/or bleeding. The mean age of this population was 65.5 years (range = 26 – 95), with 55% (n=11) being older than 65 years.

There were 11 serious renal events reported during this same period. The mean age of the 8 patients whose age was reported was 55.8 years (range = 17-90). Of these, 4 were greater than 65 years.

The reporting frequency of serious GI and renal events during this 6-year period was low, even in the elderly. Although those > 65 years comprised approximately 50% of the serious events reported, it is important to note that, in the general population, the risk of developing serious GI and renal events increases with age.

### **Conclusions on GI and Renal Safety Data in Patients > 65 years**

Based on data from a variety of sources, including controlled clinical trials, epidemiology studies, and actual consumer use, older consumers do not appear to be at an increased risk of an adverse outcome when ibuprofen is administered at OTC doses and for a short duration of use (i.e., up to 10 days).

### **VII. COMMENTS ON PROPOSED NEW LABEL WARNING “ASK A DOCTOR BEFORE USE IF YOU HAVE HIGH BLOOD PRESSURE/TAKING A DIURETIC”**

While data from controlled clinical trials clearly indicate that higher prescription doses of ibuprofen taken for extended periods of time can antagonize the effects of antihypertensive drugs, the available information suggests that OTC doses of ibuprofen (1200 mg/day) can be taken safely for short periods of time.

A search of the literature between January 1, 1987 and September 25, 2002 for drug interactions between ibuprofen and antihypertensive agents (including diuretics, ACE inhibitors, beta-blockers, and calcium channel blockers) resulted in a total of 22 relevant manuscripts. Of the 22 articles, 18 were well controlled clinical trials, 2 were meta-analyses, one was a case report, and one was a review article. Ten of the clinical trials evaluated the concomitant use of ibuprofen and diuretics and are presented in Table 2.<sup>21,27-35</sup> Five of the clinical trials evaluated the concomitant use of ibuprofen and other anti-hypertensive medications (Table 3)<sup>36-40</sup>, and three trials evaluated the concomitant use of ibuprofen and multiple antihypertensive medications (Table 4).<sup>41-43</sup>

Only 8 of the 18 trials investigated the concomitant use of OTC doses of ibuprofen and antihypertensive medications.<sup>21,27,33,37,39-41,43</sup> Furthermore, in 3 of these studies, medications

were administered for up to 4 weeks, significantly longer than the approved duration of OTC use (10 days).<sup>33,39,41</sup> Nevertheless, the results of these studies showed that ibuprofen either had little or no effect on the antihypertensive agent under study, suggesting that OTC ibuprofen can be taken concomitantly with antihypertensive medications.

As is the case with renal and GI safety, the two meta analyses showed that, as a class, NSAIDs may elevate blood pressure in patients receiving antihypertensive medication, but the magnitude of this interaction varies among NSAIDs. Importantly, ibuprofen did not significantly affect blood pressure in either meta analysis.<sup>45-46</sup>

**Table 2. Published Studies Evaluating the Concomitant Use of Ibuprofen and Diuretics**

Citation/ Study Design	Antihypertensive Dose	IBU dose/ duration	Sample Size	Primary Variables	Conclusion(s)
Clark, 1994 <sup>27</sup> x-over, pbo controlled	Hydrochlorothiazide 100 mg	1200 mg/ 3 days	Total = 5 young healthy subjects	Urine volume, Na excretion, free water clearance	<b>IBU decreased urine volume, free water clearance compared to HCTZ alone</b>
Cummings, 1988 <sup>28</sup> Parallel group, randomized	~40% of subjects on diuretics, mostly Hydrochlorothiazide 50 mg	1600 mg/ 6 weeks	Total =24 elderly subjects with arthritic conditions	Blood pressure, body weight, weekly serum creatinine and BUN	IBU had no effect on blood pressure, weight, serum creatinine, or BUN
Davies, 1988 <sup>29</sup> x-over, double- blind, pbo- controlled, randomized	Bendrofluazide 2.5 – 10 mg	1600 mg/ 2 weeks	Total =7 mild –moderate HTN	Blood pressure, pulse, heart rate, plasma renin activity, body weight	In untreated hypertension, IBU had no effect on blood pressure; ibuprofen also had no effect on the antihypertensive efficacy of bendrofluazide
Epstein, 2000 <sup>30</sup> x-over, open label	Furosemide 20mg	1800mg/ 3 days	Total = 8 (young, healthy subjects)	Blood oxygen level- dependent MRI	IBU had no effect on peak diuresis or on the increase in medullary oxygenation produced by furosemide
Furey, 1993 <sup>21</sup> double-blind, parallel, randomized	Hydrochlorothiazide 50 mg	1200mg/ 7 days	Total = 25 elderly with mild HTN and mild renal insufficiency	Blood pressure, body weight	<b>IBU had no effect on the antihypertensive efficacy of hydrochlorothiazide</b>
Gurwitz, 1996 <sup>31</sup> Double-blind, x-over, randomized Pbo controlled	Hydrochlorothiazide 25 or 50 mg	1800 mg/ 4 weeks	Total = 22 elderly with HTN	Blood pressure, mean arterial pressure (MAP)	Small but sign. Increase in supine systolic (4.2mm) and MAP (2.6mm), standing systolic (4.7mm), and MAP (3.2mm) in those who received IBU in the second period of the study (there was a sign. period effect)
Klassen, 1993 <sup>32</sup> Double-blind, parallel, randomized	Hydrochlorothiazide 50 mg	2400 mg/ 4 weeks	Total = 48 with essential HTN	Blood pressure, body weight, heart rate, mean arterial pressure at weeks 2 and 4	Small (<3mm Hg) but statistically significant increase in blood pressure and body weight at wks 2 and 4
Koopmans, 1987 <sup>33</sup> x-over, open label	Hydrochlorothiazide 50 mg	1200 mg/ 4 weeks	Total = 9 with essential HTN	Blood pressure, body weight, plasma renin activity, mean arterial pressure at weeks 2, 4	<b>No effect on blood pressure at week 2; plasma renin activity decreased, body weight increased with IBU</b>
Passmore, 1989 <sup>34</sup> x-over, double- blind, pbo controlled	Furosemide 20 mg iv	1600 – 2400 mg/ 3 days	Total =16 normotensives 8=1600 mg/day 8=2400 mg/day	GFR, plasma renin activity, renal blood flow, urinary electrolyte excretion	IBU inhibited furosemide induced diuresis and plasma renin activity; effect was not dose dependent
Wright, 1989 <sup>35</sup> x-over, double- blind, pbo-control, randomized	Hydrochlorothiazide 50 mg	3200 mg/ 8 days	Total = 12 middle aged women with essential HTN	Blood pressure, body weight, urinary sodium, creatinine and PGE2	IBU had no effect on the antihypertensive efficacy of hydrochlorothiazide

HTN = Hypertension; MAP = mean arterial pressure; GFR = glomerular filtration rate; SBP = systolic blood pressure;  
 DBP = diastolic blood pressure

**Table 3. Published Studies Evaluating the Concomitant Use of Ibuprofen and Angiotensin-Converting Enzyme Inhibitors, Beta-Blockers, or Calcium Channel Blockers**

Citation/ Study Design	Antihypertensive dose	Ibuprofen dose/duration	Sample Size	Primary Variables	Conclusion(s)
Fommei, 1987 <sup>36</sup> x-over	Captopril 25 mg single dose	800 mg single dose	Total=7 3 renovascular HTN 4 essential HTN	GFR, Plasma renin activity at 90 min post-dose	Captopril-induced decrease in GFR potentiated by ibuprofen in renovascular hypertensives; No other effects noted
Minuz, 1987 <sup>37</sup> Open label, parallel group	Enalapril 20 mg/ 4 days	<b>1200 mg/ 2 days (days 3 and 4)</b>	Total = 16 essential HTN low Na diet=8 high Na diet=8	Blood pressure, plasma aldosterone, plasma renin activity	<b>Ibuprofen had no effect on the antihypertensive efficacy of Enalapril</b>
Davies, 1988 <sup>38</sup> x-over, double- blind, randomized, pbo-controlled	Propranolol 120-360 mg	1600 mg/ 2 weeks	Total =8 mild- moderate HTN	Blood pressure, body weight, heart rate, plasma renin activity	In untreated hypertension, ibuprofen had no effect on blood pressure; Ibuprofen also had no effect on the antihypertensive efficacy of propranolol
Houston, 1995 <sup>39</sup> Double-blind, pbo-controlled, randomized	Verapamil SR 240 or 480 mg	<b>1200 mg/ 3 weeks</b>	Total =53 HTN	Blood pressure	<b>Ibuprofen had no effect on the antihypertensive efficacy of verapamil</b>
Minuz, 1995 <sup>40</sup> x-over, single- blind, placebo controlled, randomized	Amlodipine 10 mg	<b>1200 mg/ 3 days</b>	Total = 12 Mild or moderate HTN	Blood pressure, heart rate, plasma renin activity	<b>Ibuprofen increased mean systolic BP (+7.8mm Hg), Diastolic BP (+3.9 mm Hg) Ibuprofen had no effect on vascular resistance</b>

HTN = Hypertension; MAP = mean arterial pressure; GFR = glomerular filtration rate; SBP = systolic blood pressure; DBP = diastolic blood pressure

**Table 4. Published Studies Evaluating the Concomitant Use of Ibuprofen and Multiple Anti-Hypertensives**

Citation/ Study Design	Antihypertensive/ Dose	Ibuprofen Dose/Duration	Sample Size	Primary Variables	Conclusion(s)
Radack, 1987 <sup>41</sup> Double-blind, PBO-controlled, parallel, randomized	Multiple	1200 mg/ 3 weeks	Total = 12; Diuretic + beta- blocker = 5 Diuretic + adrenergic antagonist = 6 Diuretic, beta blocker + vasodilator = 1	Blood Pressure, Mean Arterial Pressure	No effects noted at week 1; after 3 weeks, mean diastolic blood pressure rose by 6.4mm Hg (95% CI=1.05, 11.75; p<0.02).
Thakur, 1999 <sup>42</sup> x-over	Fosinopril 10-40 mg Hydrochloro- thiazide 25 mg	2400 mg/ 1 month	Total = 17 hypertensive women > 65 yrs	Blood Pressure, Mean Arterial Pressure, Na/Cr	No effects noted for ibuprofen
Pancera, 1996 <sup>43</sup> Randomized, single- blind	Amlodipine 10 mg or Lisinopril 20 mg	1200 mg/ 3 days	Total = 20 hypertensive males	Blood Pressure, Heart Rate, arterial resistance	<b>Slight but significant increase in systolic BP (+4.25 mm Hg), no other effects noted.</b>
Elliot, 1995 <sup>44</sup> Case study	Furosemide 80 mg Lisinopril 40 mg	2400 mg/ 3 months	56 year-old male	Blood Pressure	SBP, DBP increased over the course of ibuprofen treatment, with worsening signs of heart failure. Measures returned to baseline level after ibuprofen treatment ended

HTN = Hypertension; MAP = mean arterial pressure; GFR = glomerular filtration rate; SBP = systolic blood pressure; DBP = diastolic blood pressure

**VIII. IBUPROFEN USE AND CONGESTIVE HEART FAILURE**

It has been theorized that by inhibiting renal prostaglandin synthesis, NSAIDs adversely affect congestive heart failure (CHF) by causing sodium and water retention. Accordingly, several members of NDAC voiced support for the inclusion of a warning against NSAID use in patients with congestive heart failure (CHF) at the September 20th meeting, although a formal vote on this specific warning was not taken at the meeting.

Despite the commonly held view that NSAIDs increase the risk of CHF, an extensive literature search showed that there is very little data on the relationship between ibuprofen and CHF, especially when ibuprofen is taken under OTC conditions.

In a review of the 5,000-patient rofecoxib osteoarthritis database, Gertz, et al. concluded that the renal safety profile of the COX-2 inhibitor was generally similar to that of the comparator non-selective NSAIDs (ibuprofen/nabumetone/diclofenac). In this database, a total of 847 patients had taken ibuprofen 2400 mg/day for periods of up to six months, and the incidence of congestive heart failure was noted to be rare.<sup>47,48</sup>

In another study to examine the incidence of thromboembolic events in patients treated with celecoxib (n=3,987), ibuprofen 2400 mg/day (n=1985), or diclofenac (n=1,996), it was again noted that there was no difference between the treatment groups for CHF (celecoxib: n=12 [0.3%]; ibuprofen: n=9 [0.5%]; diclofenac (n=3 [0.2%])).<sup>49</sup>

An analysis of the impact of NSAIDs (specific drugs or dose/duration of use not indicated) on hospitalization rates for congestive heart failure was performed on the entire population of Sweden. The study group consisted of 17,093 patients hospitalized in 1993 with a primary diagnosis of heart failure. The adjusted relative risk of heart failure for each increase of one standard deviation of NSAID use (5.8 defined daily doses/1000 inhabitants/day) was 1.08 [95% CI 1.04, 1.12]. Although a significant association was found, the relative risk was only slightly larger than one, and these data do not demonstrate a causal relationship between NSAID use and occurrence of congestive heart failure.<sup>50</sup>

This relationship was also examined in a case-control study of 365 cases of congestive heart failure and a matched set of 658 controls. The authors concluded that use of a prescribed NSAID (again, dose or duration of use unspecified) in the week prior to admission for congestive heart failure was associated with a doubling of the odds of an admission for this diagnosis (adjusted odds ratio, 2.1; 95 CI, 1.2-3.3).<sup>51</sup>

A cohort study of 10,519 patients over 55 years old; on NSAIDs (ibuprofen-33.1%, naproxen-10.4%, indomethacin- 8.1% of prescriptions) and diuretics found that there was a two-fold increased risk of hospitalization for CHF when these two classes of drugs were combined versus use of diuretics alone. In that trial, low dose NSAID use was defined as

0-0.74 of the defined daily dose (it was not clear if the defined daily dose/day was OTC or RX), medium dose NSAID use was defined as 0.75 – 1.24 of the defined daily dose/day and high dose NSAID use was defined as > 1.24 of the defined daily dose/day (duration of use was not mentioned). A dose-response relationship was not seen, nor were there any differences in the risk of hospitalization for CHF among the different NSAIDs (ibuprofen, naproxen, indomethacin).<sup>52</sup>

The current labeling for OTC ibuprofen states, “ Ask a doctor or pharmacist before use if you are under a doctors care for any continuing medical condition.” In the absence of data directly addressing the effect of OTC ibuprofen on CHF, WCH believes that the general warning as is found in the current labeling is adequate.

**IX. COMMENTS ON CURRENT ALCOHOL WARNING “IF YOU CONSUME 3 OR MORE ALCOHOLIC DRINKS EVERY DAY, ASK YOUR DOCTOR WHETHER YOU SHOULD TAKE IBUPROFEN OR OTHER PAIN RELIEVERS/FEVER REDUCERS. IBUPROFEN MAY CAUSE STOMACH BLEEDING”**

It is well established that alcohol and NSAID use are independent risk factors for gastrointestinal bleeding. At the September 12<sup>th</sup> NDAC meeting, it was agreed that consumers should be warned against concomitant alcohol and OTC analgesic use only if there is data demonstrating that alcohol potentiates the risk of gastrointestinal bleeding from using OTC analgesics. Citing a lack of such evidence, the majority of the NDAC members voiced support for the removal of the alcohol warning for OTC NSAIDs and aspirin (although a formal vote on this issue was not taken). WCH agrees with the Committee and believes that the warning should be removed from the current label of OTC ibuprofen. WCH has had extensive interactions with the Agency regarding this issue. Over the past nine years, WCH has provided the Agency with 6 submissions containing data and supportive evidence indicating that the excellent gastrointestinal tolerability of ibuprofen, particularly at nonprescription doses, is undiminished when the drug is taken by individuals who regularly consume alcohol.

The following is an updated review of the published literature evaluating the risks associated with the concomitant use of alcohol and ibuprofen.

### **Endoscopy Study**

Lanza et al. demonstrated that the excellent GI tolerability seen with ibuprofen in endoscopy studies is not affected by concomitant alcohol use.<sup>53</sup> These investigators conducted a double-blind, placebo-controlled study among 60 normal volunteers, comparing the mucosal tolerability of 3 ounces of 100-proof vodka given four times daily (equal to 180 g ethanol) administered concomitantly with aspirin 3900 mg/day or ibuprofen 2400 mg /day (i.e., twice the nonprescription maximum). After one day of these regimens, endoscopy was performed. Ibuprofen without alcohol and placebo without alcohol had similar gastric mucosal tolerability, while both were significantly better than aspirin. Ibuprofen 2400 mg with alcohol was not significantly different from ibuprofen without alcohol. Therefore, even at a prescription dose that is twice the OTC maximum, alcohol had no significant effect on the mucosal tolerability of ibuprofen.

### **Clinical Trials**

A study in 12 healthy volunteers was undertaken to determine the effect of ibuprofen (800 mg) on the single-dose kinetics of alcohol. It was determined that ibuprofen had no effect on the kinetics of alcohol when administered one hour before alcohol.<sup>54</sup>

Pulanic conducted a prospective study to determine the effect of ibuprofen and other NSAIDs in patients with pre-existing bleeding peptic ulcers and erosions. They considered such factors as alcohol history and found no association between ibuprofen and alcohol use.<sup>55</sup>

### **Epidemiology Studies**

Epidemiologic investigations have also examined the effect of concomitant ibuprofen and alcohol use on the risk for gastrointestinal bleeding. Carson et al. analyzed whether an alcohol-related diagnosis affected the incidence of upper gastrointestinal bleeding among

Medicaid patients.<sup>56</sup> Patients with an alcohol-associated diagnosis who took prescription ibuprofen had no material increase in bleeding incidence compared to the population as a whole. The odds ratio for upper GI bleeding among ibuprofen users with an alcohol-related diagnosis compared to the entire population of ibuprofen users was 1.34 (95% confidence interval = 0.42-4.28). These results indicate that concomitant alcohol abuse did not increase the GI bleeding risk among prescription ibuprofen users.

A study by Kaufman et al. examined the effect of alcohol intake on a population that was recruited from Stockholm, Budapest, and Massachusetts.<sup>57</sup> The relative risk of bleeding was not significantly increased for the occasional ibuprofen user (defined as taking ibuprofen less than every other day) who also drank alcohol (RR = 1.2, 95% CI, 0.8 – 1.7). For those who took ibuprofen on a regular basis (defined as at least every other day for a period of at least ~4 weeks), the risk was 2.7 (1.6 – 4.4). However, this result was primarily driven by the spurious finding that regular ibuprofen users whose alcohol intake was < 1 drink per week had a high relative risk of 4.4 (1.8-11). The estimated relative risks for regular users of ibuprofen at various other levels of alcohol intake (1-6 to > 21 drinks/week) showed that there was no consistent trend between relative risk and increasing alcohol use, with very few regular users of ibuprofen in the heavier drinking categories. Due to a lack of data, the authors indicate that further evaluation of the relationship between ibuprofen and alcohol use is required before any conclusions can be made about risk of GI bleeding.

Neutel studied the effect of alcohol abuse on the risk of NSAID-related gastrointestinal events using data from the Saskatchewan Health Database from 1976 to 1986 (prior to the availability of OTC ibuprofen).<sup>58</sup> In this case control study of 1083 patients and 14,754 controls, the use of prescription ibuprofen and/or naproxen without alcohol use led to an odds ratio of 1.9, whereas alcohol abuse by itself led to an odds ratio of 2.6. The presence of both prescription ibuprofen and/or naproxen and alcohol led to an odds ratio of 6.5. It is important to note that the presence of alcohol abuse in this study was defined as having a record of any alcohol related treatment or through filling prescriptions for

disulfiram. The authors note that by the time that treatment is administered for alcoholism, the alcoholism is usually a long term chronic condition with long term sequela, even after drinking has stopped. Accordingly, the results of this study cannot be compared to studies that have measured the daily alcohol exposure (as well as NSAID exposure) just prior to the GI event. **The authors noted that studies which used this latter approach have shown that alcohol and NSAID use are independent risk factors for GI bleeding.**

#### **Conclusions on Current Alcohol Warning**

Taken together, data from clinical trials as well as epidemiological studies show that alcohol does not adversely affect the GI safety of ibuprofen, indicating that the alcohol warning for ibuprofen products is not warranted by the scientific evidence.

#### **X. OVERALL CONCLUSIONS**

WCH agrees with the Agency's proposal to include ibuprofen 200 mg tablets in the Tentative Final Monograph for IAAA drug products for OTC use. The Agency's proposal is based, in part, on the very favorable safety profile that OTC ibuprofen has exhibited since it first became available to consumers in 1984. WCH believes that this long history of safe and effective use indicates that the current OTC label has been effective in communicating the appropriate use of the product. Included in this submission are the results of a recently conducted label comprehension study which confirms that the communication goals of the label are very successfully met.

As part of the proposed rule to include ibuprofen in the TFM, the Agency has suggested several new label warnings. The safety of OTC NSAIDs was also recently discussed at a joint meeting held between the FDA and NDAC. At that meeting, NDAC also made some recommendations regarding label changes. WCH believes that any changes to the current label should be based on safety data from ibuprofen, taken at OTC doses and duration of use. After a thorough review of the available data from a variety of sources, including clinical trials, epidemiology studies, and safety surveillance data, WCH does

not believe that there is sufficient data warranting the following additions to the current label:

- “Ask a Doctor Before use if you have stomach problems that last or come back, such as heartburn, upset stomach, or pain”
- “Ask a Doctor or Pharmacist before use if you are over 65 years of age”
- “Ask a Doctor before use if you have high blood pressure/are taking a diuretic”
- “Ask a Doctor before use if you have congestive heart failure”

Finally, WCH has provided data showing that alcohol does not adversely affect the GI safety of ibuprofen (as was discussed at NDAC), which indicates that the current alcohol warning for ibuprofen products is not warranted by the scientific evidence. Accordingly, this warning should be removed from the current label.

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**Appendix I**



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September 3, 2002

**NDAC Meeting on NSAIDs (9/20/02)**

Sandra Titus, PhD  
Advisors and Consultants Staff  
FDA/CDER  
5630 Fishers Lane  
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Dear Dr. Titus:

Reference is made to the NDAC Advisory Committee Meeting to be held on September 20, 2002. Reference is also made to the specific instructions to Open Hearing Requesters concerning the written submission of background material.

Wyeth Consumer Healthcare herein submits 50 copies of the background package for the NDAC Meeting on NSAIDs. A CD copy of the entire package in Microsoft Word is also included in this submission.

If you have any questions, please contact the undersigned at (973) 660-5753 or Mary Davis at (973) 660-5825.

Sincerely,  
WYETH CONSUMER HEALTHCARE

A handwritten signature in black ink that reads "Sharon Heddish".

Sharon C. Heddish  
Vice-President, Regulatory Affairs

**Meeting Topic: NDAC Meeting on Risks of NSAIDs**

**Background Package Submitted by  
Wyeth Consumer Healthcare**

## TABLE OF CONTENTS

Executive Summary.....	1
I. Introduction.....	4
II. Efficacy of Ibuprofen 200-400 mg .....	6
III. Ibuprofen Safety .....	10
A. Gastrointestinal Safety.....	11
B. Renal Safety .....	23
C. Safety in Overdose .....	30
IV. Development of Labeling for OTC Ibuprofen.....	30
V. Consumer Use Data .....	35
VI. Conclusions.....	36

### **Executive Summary**

A joint meeting between the FDA and the Nonprescription Drug Advisory Committee (NDAC) is scheduled for September 20, 2002. The purpose of the meeting is to discuss the gastrointestinal (GI) and renal toxicity risks associated with the use of over-the-counter (OTC) nonsteroidal anti-inflammatory drugs (NSAIDs) and to determine whether modification to the current label for these products is necessary to address these risks.

Wyeth Consumer Healthcare (WCH), the leading manufacturer of OTC ibuprofen, has prepared an overview of the vast data supporting the safety and efficacy of OTC ibuprofen. These data show that OTC ibuprofen has a long history of safe and effective use by consumers, indicating that the current labeling for OTC ibuprofen has been generally effective in communicating its appropriate use.

Based on data derived from controlled clinical trials, epidemiology studies, and safety surveillance data:

- Not all NSAIDs have the same safety profile;
- For any NSAID, the risk for developing serious events is related to dose and duration of use;
- Ibuprofen has the most favorable GI safety profile of all NSAIDs;
- The approved OTC daily dose of ibuprofen (1200 mg/day) is 37.5% of the maximum daily prescription dose (3200 mg); the OTC dosing regimen of 200 mg to 400 mg has been shown to provide very effective analgesia and is designed to allow for flexibility in dosing where necessary;
- When OTC doses of ibuprofen (200-400 mg/dose; 1200 mg/day) are taken for acute episodes of pain (i.e., up to 10 days), its GI safety profile is even more favorable than at prescription doses, with an extremely low risk of causing serious gastrointestinal events;

A meta-analysis of epidemiology studies has shown that when administered at daily doses of 1500 mg-1800 mg, ibuprofen has a relative risk of GI adverse events that is not significantly different from that of the general population (RR=1.42, 95% CI 0.93, 2.15);

A case-cohort study specifically designed to estimate the relative risk of GI bleeding associated with OTC doses of naproxen sodium and ibuprofen evaluated events which occurred within the first 2 weeks of dosing among those Medicaid patients whose average daily dose was  $\leq 600$  mg/day of naproxen sodium or  $\leq 1200$  mg/day of ibuprofen. The analysis showed that the incidence of GI bleeding associated with both drugs was extremely low (0.012% for ibuprofen and 0.026% for naproxen sodium);

Over the 18 years that ibuprofen has been available OTC, the Agency has received an average of approximately 18 reports per year of GI perforations, ulcers or hemorrhage associated with OTC ibuprofen;

- The frequency of renal side effects with OTC ibuprofen has also been shown to be low (less than 2 cases of renal failure per year), confirming that nonprescription ibuprofen is well tolerated;
- Even though for the past eighteen years non-prescription (OTC) ibuprofen has been subject to the same post-marketing surveillance activities required for prescription drug products, no new, significant health risks to the OTC population have been identified;
- According to data collected and reported by the American Association of Poison Control Centers (AAPCC) from 1987 through 2000, ibuprofen poses significantly less risk than acetaminophen with respect to overdose. Ibuprofen exposures have also resulted in considerably less severe outcomes, and many fewer deaths than acetaminophen.

The excellent safety profile of OTC ibuprofen, generated over 18 years of use by millions of consumers indicates that the current labeling for OTC ibuprofen has been effective in informing consumers of the appropriate conditions for using the product. Consumer use data suggests that the vast majority of consumers follow ibuprofen's label:

- Data from a 2002 Gallup survey indicate that consumers of OTC ibuprofen use an average of only 17.1 pills per month; only 6.5% use  $> 50$  pills/month;
- In a 1996 Attitude and Usage study conducted over a 10-day period, the average number of tablets taken per dose was approximately 2, the average number of tablets taken per day was 3.6 (~720 mg); more than 6 tablets per day ( $>1200$  mg) were taken only 8% of the time.

In preparation for the September NDAC meeting, on August 23, 2002, the Agency published its review of the GI and renal safety data for ibuprofen. In their conclusion, the Agency has suggested that modifications to ibuprofen's label are warranted. On August 21, 2002, the Agency published a proposal in the Federal Register recommending that ibuprofen be included in the Tentative Final Monograph for OTC internal analgesic drug products, thereby recognizing it as being generally safe and effective. Importantly, the Agency made its recommendation based on ibuprofen's favorable safety profile, which has been generated with the **current** OTC label. As part of the Agency's proposal, they have also provided explicit wording for more specific GI and renal warnings to the label. As with the label comprehension study conducted in 1983 prior to the approval of OTC ibuprofen, greater specificity in the warnings statements may not necessarily prove to be as effective as the current more general warnings. As such, WCH strongly recommends that any proposed modifications to the label should be adequately tested to ensure the proposed changes actually benefit the consumer. Although WCH has not had sufficient time to consumer test or evaluate all of the proposed modifications, WCH is fully committed to working with the Agency on improving the label for all OTC analgesic products, including ibuprofen, where necessary.

## **I. Introduction**

A joint meeting between the FDA and the Nonprescription Drug Advisory Committee (NDAC) is scheduled for September 20, 2002. The purpose of the meeting is to discuss the gastrointestinal (GI) and renal toxicity risks associated with the use of over-the-counter (OTC) nonsteroidal anti-inflammatory drugs (NSAIDs) and to determine whether modification to the current label for these products is necessary to address these risks.

Ibuprofen is a phenylpropionic acid NSAID introduced into the United States in 1974 as a prescription product intended to treat arthritic conditions at daily doses of up to 2400 mg. It was subsequently approved for daily doses of up to 3200 mg/day, and then as a prescription drug to treat mild to moderate pain in 1978.

Since it became available to consumers in 1984, over 100 billion 200 mg tablets of ibuprofen have been sold OTC in the United States alone. Today, consumption of OTC ibuprofen accounts for approximately one third of the market for OTC analgesics. According to a 2002 study by Kauffman et al., ibuprofen continues to be one of the most commonly used drugs in the United States.<sup>1</sup>

In preparation for the September NDAC meeting, on August 23, 2002, the Agency published its review of the GI and renal safety data for ibuprofen. In their conclusion, the Agency has suggested that modifications to ibuprofen's label are warranted. On August 21, 2002, the Agency published a proposal in the Federal Register to amend the tentative final monograph (TFM) for OTC internal analgesic, antipyretic and antirheumatic drug products to include ibuprofen as a generally recognized safe and effective analgesic/antipyretic active ingredient for OTC use. The Agency based its recommendation on the very favorable safety profile of OTC ibuprofen. WCH believes that this long history of safe and effective use of OTC ibuprofen indicates that the current OTC labeling has been effective in communicating the appropriate use. As part of their proposal however, the Agency has recommended the addition of more specific GI and renal warnings to the label. For the committee's benefit, WCH has presented the Agency's proposed label changes in this document as part of the overview of the development of the current OTC label. WCH looks forward to discussing

the proposed changes with the Agency and welcomes the opportunity to further explore ways to improve the current label for OTC ibuprofen. As with the label comprehension study conducted in 1983 prior to the approval of OTC ibuprofen, greater specificity in the warnings statements may not necessarily prove to be as effective as the current more general warnings. Accordingly, WCH believes that prior to implementation, any proposed changes must be carefully tested to ensure they achieve the desired communication objective.

Ibuprofen's mode of action, like that of all NSAIDs, is related, in part, to its ability to inhibit cyclooxygenase, and therefore, prostaglandin production. Prostaglandins play an important role in inflammatory processes and pain. They are also involved in maintaining the integrity of the upper gastrointestinal mucosa, and maintaining renal function. NSAIDs clearly provide a therapeutic benefit to the vast majority of individuals. However, in rare instances, usually at prescription doses, they may also produce GI toxicity, including bleeding, ulceration, and perforation, and renal side effects, including renal failure and interstitial nephritis. Accordingly, labeling for all prescription NSAIDs includes detailed warnings describing these risks. While it is clear that such class warnings are appropriate for prescription products, it has become even more clear over the many years of prescription NSAID use that: a) not all NSAIDs have the same safety profile; and b) for any given NSAID, the risk for developing serious events is related to dose and duration of use.

Based primarily on its very favorable GI safety profile at prescription doses, ibuprofen became the first prescription NSAID to be approved by the FDA for OTC use as an analgesic in 1984. At the time of the deliberations that led to its switch, it was anticipated that ibuprofen would demonstrate an improved GI safety profile when used at lower doses over brief periods of time. Accordingly, it was approved for use at single doses of 200-400 mg, up to a maximum of 1200 mg per day. It is important to note that the OTC dose is 37.5% the minimum daily prescription dose. Like the other currently marketed monographed analgesics, the maximum duration for use was limited to 10 days (the duration of use for prescription NSAIDs is not limited).

Since ibuprofen's approval for consumer use, Wyeth Consumer Healthcare (WCH), the leading manufacturer of OTC ibuprofen, has continued to evaluate and assess the efficacy and safety profile of ibuprofen to expand the knowledge base of the effects and consequences of using ibuprofen under OTC conditions. Accordingly, WCH has prepared this document to provide the Agency and the Committee with: a) an overview of the data supporting the safety and efficacy of OTC ibuprofen, b) a history of the development of the current OTC label, and c) consumer use data on OTC ibuprofen.

The data confirm that ibuprofen is the safest prescription NSAID available, although all NSAIDs demonstrate an increased risk of adverse events when used chronically at higher prescription doses. More importantly, as originally expected, when ibuprofen is taken according to the labeled OTC dose and duration of use, the safety profile is even better. There are data to show that even at these low doses, OTC ibuprofen is highly effective in numerous pain states and is more effective than acetaminophen. The labeled dosing instructions, "take 1 (200 mg) tablet every 4 to 6 hours; if pain or fever does not respond to 1 tablet (200 mg), 2 tablets (400 mg) may be used, but do not exceed 6 tablets in 24 hours" allow for flexibility in dosing where necessary, and are supported by data demonstrating a dose-response relationship between 200 mg and 400 mg. As will be shown later in this document, consumer behavior data confirms that the vast majority of consumers follow these instructions.

## **II. Efficacy of Ibuprofen 200-400 mg**

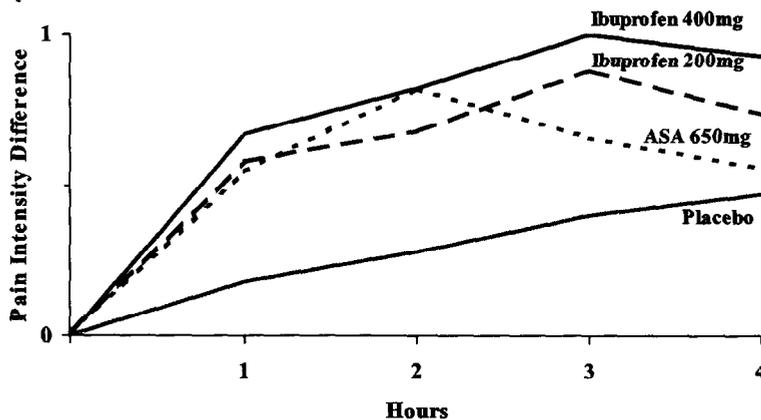
Over its 24-year history of prescription and OTC use, ibuprofen has been studied in numerous clinical analgesic trials encompassing a wide variety of pain conditions including oral surgery pain, general surgery pain, minor arthritic pain, orthopedic pain, muscle aches, sore throat, tension headache, migraine headache and dysmenorrhea. The OTC dosage regimen of 200-400 mg has been evaluated in many of these studies.

Studies in several pain models have shown that ibuprofen 200-400 mg demonstrates a clinically meaningful, as well as statistically significant dose-response relationship (Figures 1-3).<sup>2-5</sup> Both doses provide effective concentrations (EC<sub>50</sub>) of 6-10 ug/mL<sup>6,7</sup> within the first

30 minutes and reach peak effects in approximately 1-2 hours. The 400 mg dose provides enhanced analgesia that is reflected in both a greater peak effect and a slightly longer duration of effect compared to the 200 mg dose. The peak analgesic effect appears to be at or near 400 mg (Figure 4).<sup>7</sup> When evaluating the switch of ibuprofen from prescription to OTC status, an important consideration in assessing the benefit/risk of ibuprofen was evaluating efficacy above the traditional 400 mg dose. A review of the data substantiates that 400 mg of ibuprofen achieves the maximum peak analgesic effect, as higher doses only slightly enhance its duration of action.<sup>7-9</sup>

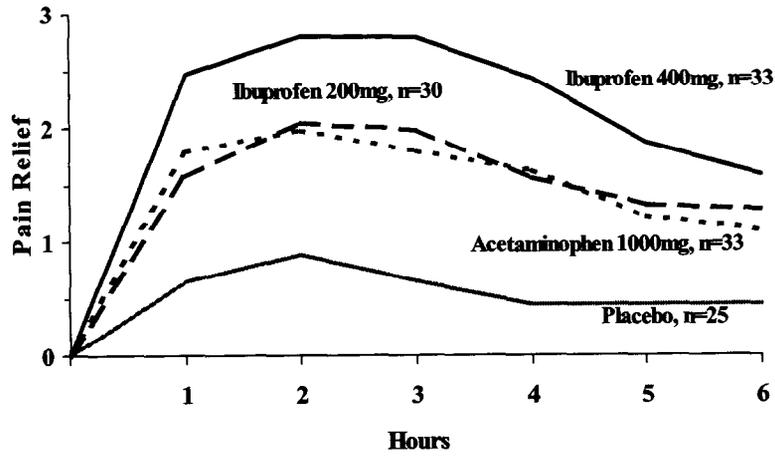
Figure 1

Cooper et al., 1977  
Oral Surgery  
40 patients/treatment



**Figure 2**

Beaver et al., 1987  
Oral Surgery



**Figure 3**

Codispoti et al., 2001  
Migraine headache  
Severe Baseline Pain Subgroup

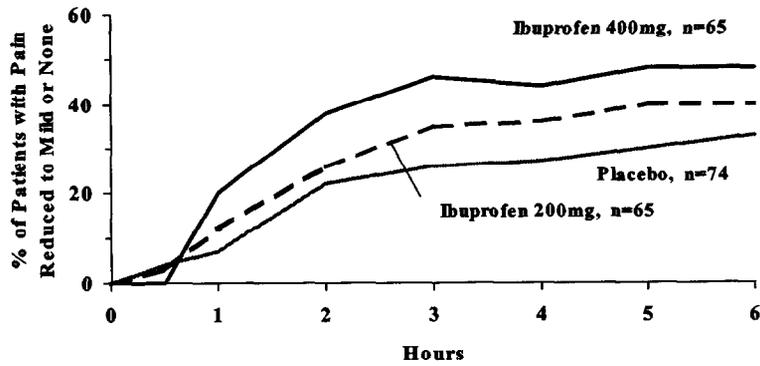
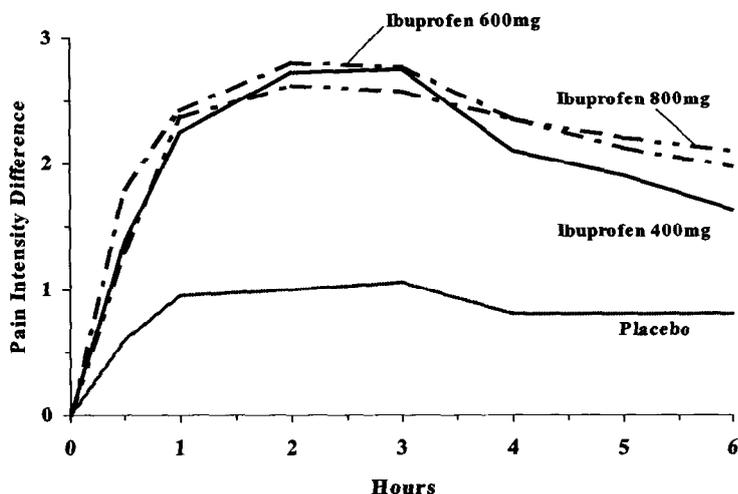


Figure 4

Laska, Sunshine et al., 1986  
Oral Surgery  
N = 195



Many of the acute pain studies evaluating ibuprofen have been performed with the Dental Impaction Pain Model. This model is widely accepted by expert analgesiologists as the most sensitive, valid and reliable paradigm for assessing relative efficacy and dose-response of NSAID analgesics. Briefly, these studies demonstrate that:

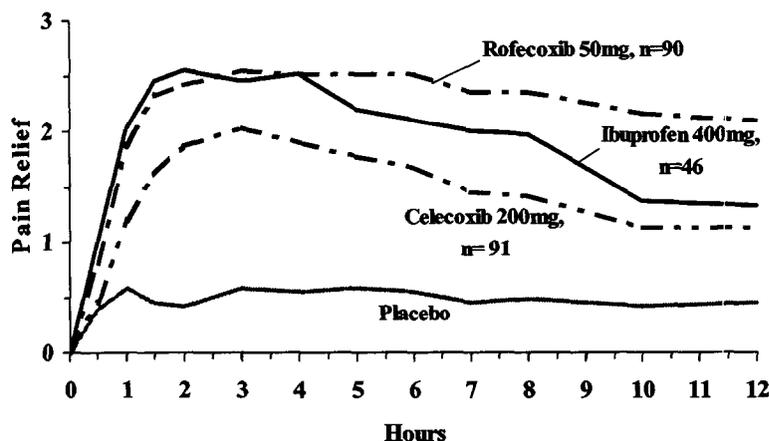
- Ibuprofen 400 mg is significantly more efficacious than both aspirin 650 mg<sup>2,10</sup> and acetaminophen 1000 mg<sup>11</sup> (Figures 1-2); its benefit is even more impressive in subjects with severe baseline pain<sup>12</sup>;
- Ibuprofen 400 mg is significantly superior to 1000 mg of acetaminophen while the 200 mg dose of ibuprofen has been shown to be equianalgesic<sup>3</sup> (Figure 2);
- Ibuprofen 400 mg has been shown to provide significantly better efficacy than acetaminophen combined with codeine,<sup>13,14</sup> and to provide comparable efficacy to other commonly used narcotic combinations.<sup>15,16</sup>

- Ibuprofen 400 mg is comparable to rofecoxib 50 mg and has statistically significant and clinically superior efficacy compared to celecoxib 200 mg over the first 4-6 hours<sup>17,18</sup> (Figure 5);
- Ibuprofen is unsurpassed by other NSAIDs (diclofenac,<sup>19</sup> ketoprofen,<sup>20</sup> naproxen sodium<sup>21,22</sup>) at their indicated analgesic doses.

In addition to the aforementioned trials in the oral surgery pain model, ibuprofen 200-400 mg has also been shown to be highly effective, and significantly superior to aspirin or acetaminophen in headache pain,<sup>23,24</sup> sore throat,<sup>25</sup> sports injuries<sup>26</sup> and episiotomy pain.<sup>27,28</sup>

**Figure 5**

Malmstrom et al., 1999  
Oral Surgery (impaction)



Ibuprofen has been proven efficacious for a broad variety of painful conditions. It has a positive dose-response with a higher analgesic ceiling than either aspirin or acetaminophen. These characteristics allow for a flexible dosing regimen so that drug exposure can be titrated to the intensity and duration of the pain being treated.

### **III. Ibuprofen Safety**

The safety data that have been generated since ibuprofen became available as an OTC analgesic in 1984 are derived from the following sources:

- Clinical trials conducted by Wyeth Consumer Healthcare (WCH);
- Published literature on the safety and efficacy of ibuprofen;
- Post-marketing surveillance databases;
- Exposure data from the American Association of Poison Control Centers.

It is important to note that the post-marketing safety surveillance database for OTC ibuprofen is quite extensive. Given ibuprofen's NDA status, all adverse drug experience reports received by the manufacturer since its approval OTC in 1984 have been submitted to FDA. In contrast, because aspirin and acetaminophen are monographed drugs, their manufacturers are not required to submit adverse event reports to the Agency.

#### **A. Gastrointestinal Safety**

At the time of the deliberations that led to the switch of ibuprofen from prescription to OTC status in 1984, the gastrointestinal (GI) safety of the drug was thoroughly reviewed and has remained under close surveillance ever since. There is a vast body of evidence, including data from controlled clinical trials, epidemiology studies, and actual consumer use spanning 18 years, which show that: a) while there is an increased risk of experiencing serious GI events when ibuprofen is taken at prescription doses on a chronic basis, ibuprofen has the most favorable GI safety profile of all prescription NSAIDs; b) when administered at OTC doses and for a short duration for use (i.e., up to 10 days), the GI safety profile of ibuprofen is even more favorable, with an extremely low risk of causing serious gastrointestinal events, and c) despite close surveillance, no new GI adverse effect trends have been identified since ibuprofen became available for OTC use in 1984.

#### **Controlled Clinical Studies**

The safety of ibuprofen administered at OTC doses (up to 1200 mg/day) for up to a maximum of 10 days has recently been studied in three prospective, randomized, double-blind clinical trials. While these studies had limited power to detect rare, significant adverse events, they were useful in evaluating the incidence of more

frequently occurring, non-serious side effects associated with NSAID use, such as "GI upset". The designs of these studies are summarized in Table 1.

The PAIN study, which was conducted by Moore, et al., was designed to compare the safety of ibuprofen (1200 mg/day), with aspirin (3000 mg/day) and acetaminophen (3000 mg/day) in the treatment of acute pain in 8677 patients for up to seven days.<sup>29</sup>

In that trial:

- Ibuprofen was associated with a significantly lower rate of GI complaints compared to both aspirin and acetaminophen (Figure 1);
- There were no serious GI events with ibuprofen, compared to an incidence rate of 0.14% for aspirin, and 0.1% for acetaminophen;
- The rate of discontinuation was low for all three treatments, and lowest for ibuprofen (Figure 2).

WCH has conducted two Multiple Use Safety and Efficacy Studies (MUST I and II), which evaluated the safety of ibuprofen administered at the maximum daily OTC dose (1200 mg/day) and duration for use (10 consecutive days) in subjects representative of the OTC analgesic consumer population.<sup>30,31</sup> MUST study I compared the GI safety profile of OTC ibuprofen to placebo in over 1200 subjects, while MUST study II compared OTC ibuprofen to celecoxib 200 mg/day, as well as placebo, and enrolled over 2200 subjects. As an indirect measure of blood loss, fecal samples were collected in both studies and analyzed for occult blood. The results from these trials are as follows:

- The incidence of GI symptoms for ibuprofen was no different from placebo in both studies (Figure 6). In addition, the incidence of GI symptoms for celecoxib was similar to that of ibuprofen (MUST II).
- There was one serious GI event in each study;
  - in MUST I, there was one report of GI ulcer, bleeding and diverticulitis with ibuprofen. These events were considered unrelated to ibuprofen because it was subsequently learned that the subject did not take any study medication;

in MUST II, there was one report of diverticulitis in a subject who had received ibuprofen during the trial. The event was considered unrelated to the drug since it occurred 7 days after the completion of the study;

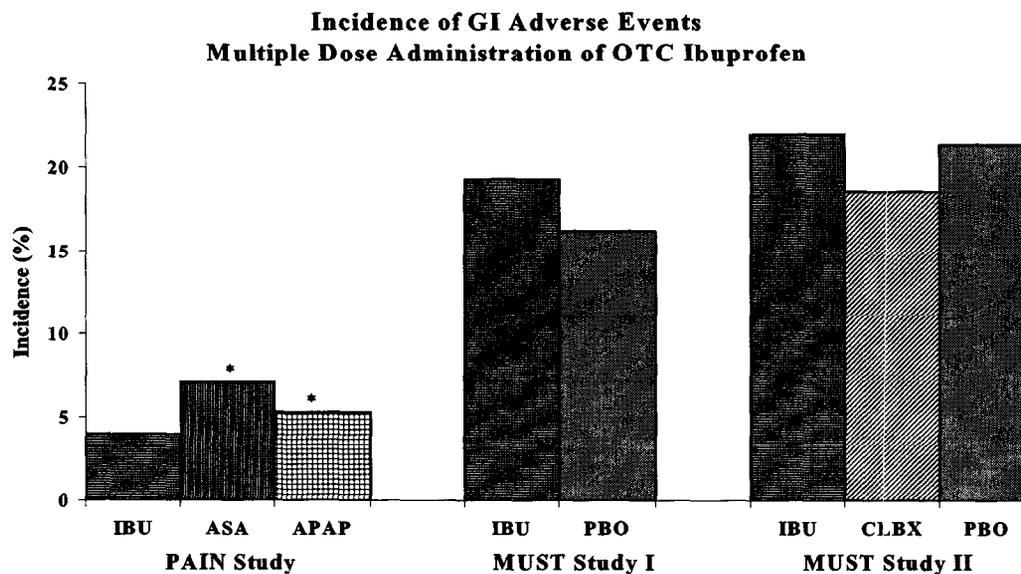
- In both trials, the incidence of subject withdrawal due to an adverse event was low, and there were no significant differences between treatment groups (Figure 7);
- In both studies, only 0.5 – 1.4% of the subjects tested positive for fecal occult blood. There were no significant differences among the treatments.

**Table 1 Overview of Multiple Dose Clinical Trials Evaluating OTC Ibuprofen Safety**

Trial	Population	Design	Treatment Groups	Duration	Sample Size
PAIN Study <sup>29</sup>	Patients 18-75 requiring short term treatment for mild to moderate pain	Randomized, double-blind, parallel group, outpatient, multiple dose	ASA 500 mg; up to 3000mg/day	1-7 days	2753
			APAP 500 mg; up to 3000 mg/day		2743
			IBU 200 mg; up to 1200 mg/day		2737
MUST Study I <sup>30</sup>	Consumers of OTC analgesics	Randomized, double-blind, parallel group, outpatient, multiple dose	IBU tablets 1200 mg/day	10 days	415
			IBU liquigels 1200 mg/day		418
			PBO		413
MUST Study II <sup>31</sup>	Consumers of OTC analgesics	Randomized, double-blind, parallel group, outpatient, multiple dose	IBU 1200 mg/day	10 days	908
			CBX 200 mg/day		891
			PBO		450

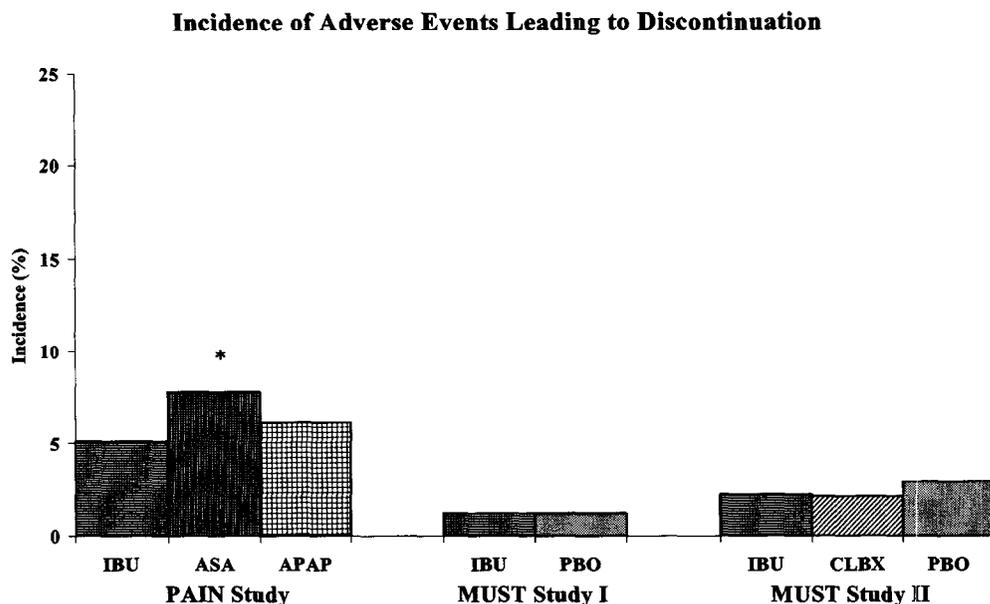
ASA = Aspirin; APAP = Acetaminophen; IBU = Ibuprofen; CBX = Celecoxib

**Figure 6**



\* Significantly worse compared to IBU

Figure 7



\*Significantly worse compared to IBU

Taken together, the PAIN and MUST studies show that the GI tolerability of low dose, short term ibuprofen use is very favorable. While the MUST Studies demonstrated that GI tolerability was comparable to placebo, the PAIN study indicated that the GI tolerability of ibuprofen was superior to aspirin, and comparable to acetaminophen. Although OTC ibuprofen is perceived by the medical community (perhaps due to their experience with prescription NSAIDs) to cause GI upset, these studies clearly demonstrate that this is not the case. Although individually, these trials had limited power to evaluate the incidence of serious events because of their limited sample sizes, taken together, with over 4400 subjects receiving ibuprofen, they do provide supportive data that the incidence of serious GI events with OTC ibuprofen is very rare and there is an absence of occult bleeding.

In addition to ibuprofen's widespread use in adults, it also has a long history of safe use in children. Ibuprofen was originally approved as a prescription drug for children in 1989, and was switched OTC in 1995. In support of its OTC switch, two large scale clinical trials were conducted, the Children's Analgesic Medicine Project (CAMP),<sup>32</sup> and the Boston Fever Study.<sup>33</sup> Both studies focused on examining the

potential risk of rare, serious events, including GI bleeding and renal failure in children treated with ibuprofen. In these two studies, over 76,000 of the 114,359 children were treated with ibuprofen, while the remaining received acetaminophen. Both studies demonstrated that there were no significant differences between ibuprofen and acetaminophen in the observed risk of GI bleeding, indicating that the treatment of children with ibuprofen for acute pain and fever is not associated with an increased risk over acetaminophen of serious GI adverse events.

In addition to the clinical trials cited above, ibuprofen has been evaluated in hundreds of other clinical trials. It has been one of the most thoroughly studied drugs on the market today. Accordingly, over the years, there have been four meta-analyses of the safety data from numerous single-dose and/or multiple-dose, randomized, double-blind clinical trials evaluating OTC doses of ibuprofen in adults.<sup>34-37</sup> These evaluations are summarized in Table 2. While there may have been some overlap in the data included in these various analyses, which consisted anywhere from 878 to 3111 ibuprofen-treated patients, they provide additional data indicating that OTC ibuprofen has an excellent safety profile in multiple-dose, as well as single-dose use. The analyses consistently show that OTC doses of ibuprofen have a frequency of GI events similar to placebo, or acetaminophen.

**Table 2 Overview of Meta-Analyses of Controlled Clinical Trials to Evaluate the Safety Profile of OTC Ibuprofen**

Author	Scope of Analysis	Treatments (sample size)	Results
Furey, et al. <sup>34</sup> (1992)	15 double-blind, randomized, placebo controlled, single dose trials	IBU 200-400 mg (n=878) APAP 650-1000 mg (n=849) PBO (n=852)	Incidence of GI AEs was comparable for all 3 treatments IBU=0.9% APAP=1.1% PBO=0.9% No serious GI AEs reported No renal AEs reported
DeArmond, et al. <sup>35</sup> (1995)	19 double-blind, randomized, single-dose and multiple-dose trials which included IBU as comparator	IBU 200-400 mg (n=1574) PBO (n=1061)	Most Common GI AE: Nausea IBU=2.2% PBO=2.1% No serious GI or Renal AEs reported
Rainsford, et al. <sup>36</sup> (1997)	96 double-blind, randomized, single-dose and multiple dose trials	IBU (n=3111) APAP (n=5958)	Incidence of GI AEs with IBU was comparable to APAP No serious GI or renal AEs reported
Kellstein, et al. <sup>37</sup> (1999)	8 randomized, multiple-dose, placebo controlled multiple-dose trials	IBU 800-1200 mg/day (n=1094) PBO (n=1093)	Incidence of GI AEs with IBU was comparable to PBO IBU=12.1% PBO=11.0% No renal AEs reported

IBU = Ibuprofen; APAP = Acetaminophen; PBO = Placebo

### Epidemiology Studies

Because of their widespread use, there have been many epidemiological studies evaluating the relationship between NSAIDs and serious GI events. Henry, et. al. recently completed a comprehensive meta-analysis of controlled epidemiological studies which used **prescription** drug databases to evaluate the relationship between NSAID use and hospital admissions for serious GI events.<sup>38</sup> The analyses included 36 case control trials and 8 controlled cohort studies which had been completed through June 2001.

- Sixteen of the case control studies included ibuprofen. The pooled relative risk of developing a serious GI event for ibuprofen in these studies was 1.81 (95% CI = 1.34, 2.43);
- Nine of the 16 studies had relative risk 95% confidence intervals which included unity;
- Figure 8 presents the results of pooling the studies which compared ibuprofen to a specific NSAID. Using ibuprofen as the reference, naproxen, diclofenac,

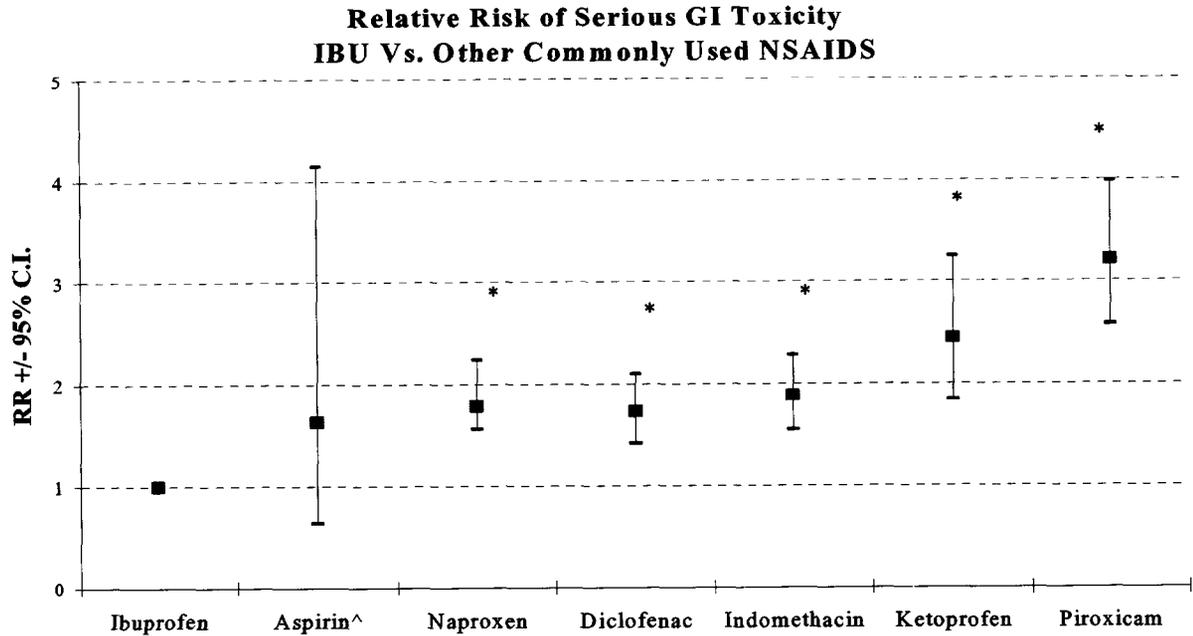
indomethacin, ketoprofen, and piroxicam all had a significantly higher relative risk than ibuprofen. Although aspirin was shown to be no different from ibuprofen in this analysis, it should be noted that in the majority of studies, aspirin was taken in low doses for cardioprotection;

- Seven studies evaluated the relative risks associated with low doses and high doses of prescription NSAIDs. Five of these studies evaluated ibuprofen. The pooled results from these 5 trials are presented in Figure 9 and indicate that the relative risk for ibuprofen at lower doses, (defined as  $\leq 1500$  mg in some studies, and  $\leq 1800$  mg in others; RR = 1.42, 95% CI 0.93, 2.15) is significantly reduced compared to higher ibuprofen doses (defined in some studies as  $\geq 1500$  mg and in others as  $\geq 1800$  mg; RR = 4.40, 95% CI 2.79, 6.92). These results showed that lower doses of ibuprofen were not associated with an increased risks of serious GI adverse events, which is especially impressive since:

The “low doses” of ibuprofen defined in these studies ( $\leq 1500$  mg/day in some studies, and  $\leq 1800$  mg/day in others) were higher than the OTC dose of 1200 mg/day;

These studies evaluated data from prescription databases, which probably included patients who were chronically taking ibuprofen, and who were also likely to have had confounding underlying disease.

Figure 8



# Studies in meta-analysis†

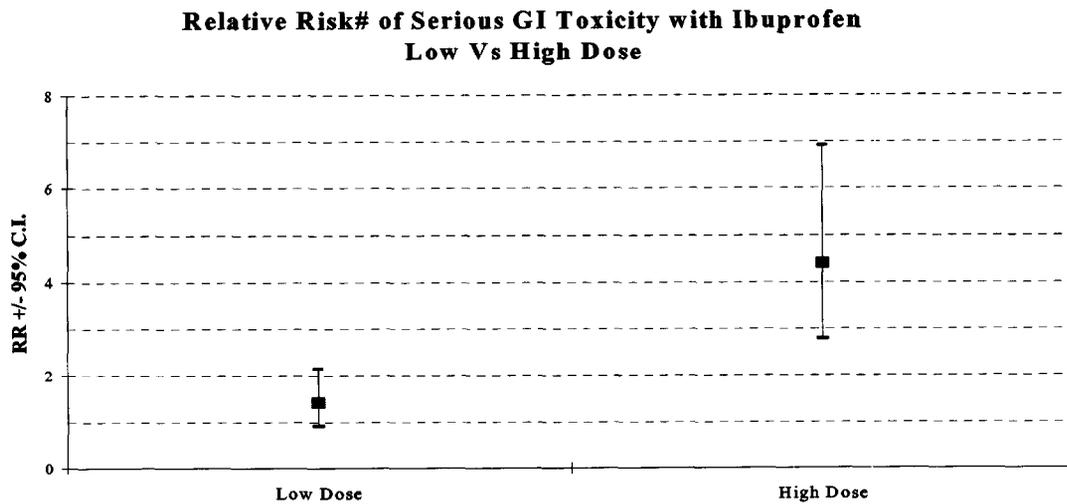
11      18      13      18      13      15

† Each Comparison was based on a meta analyses of controlled epidemiological studies which simultaneously evaluated the drug with IBU

<sup>^</sup> Majority of aspirin use was as intermittent low-doses in analgesia, or low-dose prophylaxis in CV disease

\*Significantly worse than ibuprofen at 0.05 level

Figure 9



# RR Vs non-use of any NSAID, based on a meta analysis of studies which provided data on both "Low" and "High" dose use of Ibuprofen. "Low" dose as defined within each study, and varied as  $\leq 1500$  mg, and  $\leq 1800$  mg

Using a prescription database known as ARAMIS (Arthritis, Rheumatism, and Aging Medical Information System), Singh, et al. concluded that there is an overall increased risk of developing serious GI toxicity with OTC doses of NSAIDs.<sup>39</sup> Even within this dataset based on chronic prescription use in patients with significant underlying disease, ibuprofen was reported to have a rate of GI hospitalization (per 100 patient years) of 0.65, with the 95% confidence interval included zero (95% CI 0.0, 1.38).

Blot and McLaughlin published an analysis of the American College of Gastroenterology (ACG) bleeding registry to evaluate the potential risks of gastrointestinal bleeding associated with OTC NSAIDs. The ACG bleeding registry was generated in 1995 by having members of the ACG participate in a mail survey, where they provided information in a non-randomized, non-blinded manner on up to 10 patients with GI bleeding and 10 procedure-matched patients without GI bleeding.<sup>40</sup> Of those patients in the registry who developed GI bleeding, 10.1% reported taking OTC doses of ibuprofen, compared to 5.8% of controls. The odds ratios were related to the dose of ibuprofen as follows:  $\leq 600$  mg per day had a ratio of 1.8 (95% CI 0.8, 4.1), while  $\leq 1200$  mg per day had a ratio of 3.5 (95% CI 1.2, 10.7). The relevance of these data to true OTC use of ibuprofen is unknown, since critical information regarding duration of use was not collected, and since the survey was conducted in an uncontrolled, non-randomized, non-blinded manner.

To WCH's knowledge, there are no epidemiology studies which have specifically evaluated the relative risk of OTC doses of ibuprofen administered under OTC conditions (i.e.,  $\leq 10$  days). This is probably because most databases do not track use of OTC products; therefore, the data are not accessible. However, a case-cohort study by Strom et al, was specifically designed to estimate the relative risk of GI bleeding associated with OTC doses of naproxen sodium and ibuprofen by evaluating events which occurred within the first 2 weeks of dosing among those Medicaid patients whose average daily dose was  $\leq 600$  mg/day of naproxen sodium or  $\leq 1200$  mg/day of ibuprofen.<sup>41</sup>

- The incidence of GI bleeding associated with ibuprofen was 0.012%, and 0.026% for naproxen sodium;
- Compared to ibuprofen, the adjusted relative risk for those using naproxen sodium was significantly higher, 2.0 (95% CI 1.1, 3.8).

It should be noted that the absolute risk for serious GI bleeding was extremely low for both drugs.

In addition to the Strom study, the effect of the increased availability of OTC NSAIDs on the hospitalization and mortality rates from gastrointestinal bleeding and peptic ulcer disease was evaluated by Lewis, et al.<sup>42</sup> As presented in the table below, the hospitalization and mortality rates due to these conditions have not increased concurrently with the increasing sale of NSAIDs over the years.

**Table 3 Correlations Between NSAID Sale and Rate of Hospitalization and Mortality for Peptic Ulcer Disease and GI Bleeding**

	Mortality from Peptic Ulcer Disease	Hospitalization from Peptic Ulcer Disease	Mortality from GI Bleeding	Hospitalization from GI Bleeding -
NSAIDs	-0.17, p=0.65	0.14, p=0.38	-0.67, p=0.96	-0.67, p=0.96
Aspirin	-0.31, p=0.77	0.33, p=0.21	-0.62, p=0.94	-0.74, p=0.98
NSAIDs + Aspirin	-0.24, p=0.71	0.31, p=0.23	-0.81, p=0.99	-0.88, p=0.99

In the aggregate, the vast amount of epidemiological data indicates that ibuprofen is quite safe, even at prescription doses. More importantly, from the epidemiological data that approximates OTC use, it appears that the incremental risk of serious GI events from OTC ibuprofen is extremely low relative to the background incidence of GI bleeds.

**Ibuprofen GI Safety Surveillance Data**

Data from FDA's spontaneous reporting system for all single ingredient ibuprofen products from the period May 1984 through March 2002 have been reviewed. The data presented here include only the reports of adverse events associated with the administration of ibuprofen for ten days or less, at doses of 1200 mg/day or less, and in

subjects 12 years of age or older, with no use of concomitant drugs reported (reports where any information was missing were also included). Note: The Agency's review of ibuprofen GI safety surveillance data (provided to the public on August 23, 2002) was limited to the cases reported to FDA from January 1, 1998 through December 31, 2001.

Over the 18-year period, a total of 5042 adverse event reports have been received for ibuprofen. Of these, 15.2% (n = 768) were serious, and of the serious reports, 42% (n = 324) possessed at least one GI system term (~ 18 serious GI events/year). Clinically significant reports, such as GI bleeding and perforation (n = 71) were infrequent over the 18-year reporting period. Of the 324 serious GI reports received during this 18-year period, an outcome of death was noted in four, presumably due to GI bleeding. Three of those who died were between the ages of 72-94. The age of the fourth individual was not provided. One patient had been taking 1200 mg/day of ibuprofen for an unknown period at the time of death. Dosing information for the other three deaths was not available.

When data including those who took concomitant medication were examined, there was a total of 62 deaths involving GI bleeding (including the 4 patients cited above). Twenty-five of these patients had been taking ibuprofen 1200 mg/day or less, 19 males and 6 females. Most of these patients (n=18) were  $\geq 65$  years of age, and seven had been taking aspirin concomitantly. For the remaining 37 cases, ibuprofen dosing information was not provided. Nine of these patients were male, 15 were female, and the gender of 13 patients was not provided. Of the 25 patients whose age was provided, 20 were  $\geq 65$  years old. Twelve of the 37 patients had also been taking low dose aspirin and/or another NSAID (in addition to ibuprofen).

Two decades of postmarketing experience in the United States have established that the reporting frequency of serious GI events has remained consistently low during this time, suggesting that OTC ibuprofen is well tolerated in the general population.

## **B. Renal Safety**

All NSAIDs can produce a variety of adverse effects on the kidney. While there is little threat of renal insult with NSAIDs in normal, healthy individuals, risks may be increased in the elderly, in those who are dehydrated, and in those with underlying renal disease. The risk of certain types of renal toxicity may increase with the dose and duration of NSAID use.

Almost three decades of postmarketing experience with prescription-strength ibuprofen in the United States and worldwide, during which over 100 billion doses have been administered, has shown the [reporting] frequency of renal side effects to be low. Post marketing experience with non-prescription ibuprofen confirms its safety in the general population. Safety data from controlled clinical trials add further assurance that non-prescription doses of ibuprofen are well tolerated by the kidneys.

The foregoing publicly-available information has been extracted from the original Citizen's Petition to request monograph status for ibuprofen (July 1997), and two updates (through 2001). The published OTC experience of ibuprofen during the past 18 years is consistent with a very safe profile with respect to the renal system. Despite the National Kidney Foundation's first consensus statement published in 1984, a more recent statement in 1996, and a public FDA feedback meeting on the subject, the dire renal consequences which were forecasted with the OTC availability and use of ibuprofen have not materialized. When used as directed, the potential of OTC ibuprofen to cause renal problems is extremely low.

### **Controlled Clinical Trials**

#### **Prescription Doses**

As shown in the following table, several studies indicate that under prescription use, ibuprofen is not commonly associated with adverse renal function in those without underlying renal disease. These findings suggest that, even at higher doses and longer duration of use, ibuprofen therapy is not commonly associated with adverse renal effects.

**Table 4. Controlled Clinical Trials with Ibuprofen in Patients without known Underlying Renal Disease**

Author/Year	No. Patients	Daily Dose	Duration	Outcome
Bradley, 1991 <sup>43</sup>	62	1200 mg	4 weeks	No significant effect on renal function
Cummings 1988 <sup>44</sup>	52 (63-87 years)	1600 mg	6 weeks	No significant effect on renal function
Fox, 1984 <sup>45</sup>	8412	Rx doses	in-patients = 12 days out-patients ≥ 5 Rx/yr	No significant effect on renal function
Bonney, 1986 <sup>46</sup>	182	1200-2400 mg	Up to 1 year	2 reports of elevated BUN or creatinine: clinically asymptomatic

### OTC Doses

As previously discussed under the GI Safety section of this document, the safety of ibuprofen administered at OTC doses (up to 1200 mg/day) for up to a maximum of 10 days was studied in three independent, prospective, randomized, double-blind clinical trials (the PAIN Study, MUST I and MUST II Studies).<sup>29-31</sup> While these studies individually had limited power to detect rare, significant adverse events, taken together, 4478 individuals received ibuprofen, without a single incident of a serious renal event. Similarly, in the two large scale studies that were conducted in children (CAMP and the Boston Fever Study), where over 76,000 children received ibuprofen, there was no occurrence of acute renal failure.<sup>32,33</sup>

In addition, there have been several studies conducted on the safety of OTC ibuprofen in those at risk for developing renal effects. These studies are presented in Table 5 and show that renal effects, if any, were reversible after discontinuation of drug.

**Table 5. Controlled Studies Evaluating Renal Safety of OTC Ibuprofen in At-Risk Individuals**

Author/ Year	Age/Sex or # of patients	Daily Dose	Duration	Comments/Outcome
Stosic 1995 <sup>47</sup>	55 patients with hx of reduced renal function	1200 mg	7 days	Ibuprofen caused a significant decrease in GFR and renal plasma flow.
Furey 1993 <sup>48</sup>	8 elderly patients	1200 mg	7 days	No change in renal function.
Farquhar 1999 <sup>49</sup>	12 healthy, exercised induced kidney stress	1200 mg	1 day	Ibuprofen had a small, but statistically significant effect on glomerular filtration rate compared to placebo (73.5 ± 5 vs 82 ± 5 mL/min, respectively).
Sheiner 1994 <sup>50</sup>	18/F	4 tablets (unknown)	2 days	Reduced creatinine clearance which reversed after drug was discontinued
	17/F	1200 mg	1 day	Elevated creatinine, oliguric. Reversed after ibuprofen was discontinued.

**Meta Analyses of Controlled Clinical trials**

**Prescription Doses**

A comparison of adverse renovascular experiences among 8460 osteoarthritis patients treated with the selective COX-2 inhibitor rofecoxib 25-12.5 mg/day or ibuprofen 2400 mg/day (n=1902) established that rofecoxib was generally similar to ibuprofen.<sup>51</sup> In that trial, the relative rates of renal events per 100 patient months of exposure (with 95% CI) in those who received ibuprofen were as follows:

- Acute renal failure: 0.1 (0.0, 0.2)
- Elevated serum creatinine: 0.5 (0.2, 0.8)
- Incidence of hypertension AEs: 1.3 (0.8,1.8)
- Incidence of lower extremity edema AEs: 1.7 (1.1, 2.3)

A recently published meta analysis of 14 trials by the Cochrane group reviewed the effect of NSAIDs on post-operative renal function in normal adults. The authors concluded that NSAIDs should not be withheld from adults with normal pre-operative renal function because of concerns about post-operative renal impairment.<sup>52</sup>

### **OTC Doses**

As was discussed under the GI Safety section of this document, there have been 4 meta-analyses of the safety data from numerous single-dose and/or multiple-dose, randomized, double-blind clinical trials evaluating OTC doses of ibuprofen in adults.<sup>34-37</sup> These analyses are summarized in Table 2. There were no instances of serious renal effects reported in any of these analyses, providing additional data indicating that OTC ibuprofen has an excellent renal safety profile in short term, multiple-dose, as well as single-dose use.

### **Case Reports**

To WCH's knowledge, the literature contains very few case reports of renal dysfunction associated with ibuprofen administered at OTC dosage and duration in those without underlying renal disease.

As presented in Table 6, there are 7 case reports of renal dysfunction in patients without underlying renal illness who had taken ibuprofen, but the dosage that had been taken was either higher or longer than the OTC dose. Following appropriate medical management, normal renal function was restored in all of these patients.

**Table 6. Case Reports of Renal Dysfunction in Those Without Underlying Disease Who Had Taken Ibuprofen**

Author/Year	Age/Sex	Dose	Duration	Comments/Outcome
Elasser, 1998 <sup>53</sup>	19/F	1600 mg/day	6 days	Elevated BUN, creatinine. Decreased urine output. Improvement seen after d/c ibuprofen, spironolactone.
Johnson, 1995 <sup>54</sup>	22/F	1200 mg (heavy alcohol intake the evening prior)	single dose	Elevated BUN, creatinine. Acute renal failure was reversed.
Moss, 1986 <sup>55</sup>	43/M	600 mg/day	2 days	Acute renal failure treated with hemodialysis, prednisone.
Marasco, 1987 <sup>56</sup>	45/M	800 mg/day	~ 5 weeks	Tubulointerstitial nephritis reversed after d/c ibuprofen with hemodialysis, methylprednisolone tx.
McIntire, 1993 <sup>57</sup>	12/F	600 mg, then 200 mg q6h	Unknown	Acute renal failure. Reversed.
Wattad, 1994 <sup>58</sup>	14/F	600 mg	Single dose	Nonoliguric acute renal failure. Reversed after prednisone treatment.
Fernando, 1994 <sup>59</sup>	76/M	4 tablets (unknown)	Single dose	Acute anuric renal failure. Recovered after hemodialysis
		Topical	Single dose	Acute anuric renal failure. Recovered with hemodialysis and methylprednisolone treatments

Table 7 presents two summaries of case reports and two individual case reports wherein a total of 14 patients with underlying renal disease experienced various additional renal functional abnormalities and changes associated with OTC doses of ibuprofen.

**Table 7. Case Reports of Adverse Renal Effects with OTC Ibuprofen in Those With Underlying Renal Disease**

Author/Year	Age/Sex or # of patients	Daily Dose	Duration	Comments/Outcome
Spierto 1992 <sup>60</sup>	73/M	600mg	1 week	Acute renal failure with digoxin toxicity. Reversed after discontinuation of drug.
Atkinson 1986 <sup>61</sup>	22/F	1200 mg	6 days	Elevated creatinine, acute renal failure. Reversed after ibuprofen was discontinued.
Whelton 1990 <sup>62</sup>	2 patients	2400 mg	11 days	Elevated creatinine levels, acute renal failure, asymptomatic, reversed after ibuprofen was discontinued.
Ciabottoni 1984 <sup>63</sup>	10 patients	1200 mg	1 week	Elevated mean creatinine, decreased mean creatinine clearance. Reversed after ibuprofen was discontinued.

### **Epidemiology Studies**

Many of the epidemiological studies report on NSAIDs as a class and do not report specific data for ibuprofen. Studies that specifically mention ibuprofen generally provide little information on dose or duration of use. For example, Sandler, et al. and Perneger, et al. included NSAIDs in their case control studies to examine renal dysfunction and end-stage renal disease, respectively.<sup>64,65</sup> Neither study provided specific data on dose or duration of ibuprofen use.

A study by Rexrode, et al. examined whether analgesic use is associated with a risk of renal dysfunction.<sup>66</sup> This cohort study included 11,032 previously healthy men who provided blood samples and a self-report of analgesic consumption. The main outcome measures during this 14-year study of men 40-84 years were elevated creatinine levels ( $\geq 1.5$  mg/dL), a reduced creatinine clearance ( $\leq 55$  mL/min), and self-reported use of acetaminophen, aspirin, and NSAIDs (never [ $< 12$  pills], 12-1499 pills, 1500-2499 pills, and  $\geq 2500$  pills). Mean creatinine levels and clearance were similar between the groups that used analgesics and those who did not, even in use  $> 2500$  pills. Multivariate analysis (adjusted for age, body mass, history of hypertension, elevated cholesterol, diabetes, cardiovascular disease, physical activity, use of other analgesics) indicated that the relative risks of elevated creatinine levels associated with intake of  $\geq 2500$  pills were 0.83 (95% C.I. 0.50-1.39) for acetaminophen, 0.98 (95% C.I. 0.53-1.81) for aspirin, and 1.07 (95% C.I. 0.71-1.64) for other NSAIDs. No association was observed between analgesic use and reduced creatinine clearance. The authors concluded that the moderate use of analgesics in a cohort of initially healthy men was not associated with increased risk of renal dysfunction.

Griffin, et al., reviewed the records of 1,799 patients  $\geq 65$  years old enrolled in the Tennessee Medicaid program from 1987-1991 who had acute renal failure.<sup>67</sup> Of the 1,799 patients, 18.1% were current users of NSAIDs. Ibuprofen accounted for 35% of the NSAID users. The associated risk of acute renal failure in ibuprofen users was evidenced by increasing odds ratios by dose  $\leq 1200$  mg (0.94),  $> 1200$  mg- $\leq 2400$  mg (1.89),  $> 2400$  mg (2.32).

Murray, et al. conducted a cohort study of 1908 prescription ibuprofen users and 3933 acetaminophen users from the medical records system of Indiana University Hospital during

1975-1986.<sup>68</sup> The authors included a population with multiple concomitant medical problems in an attempt to identify subgroups who might be at increased risk. Blood creatinine levels >20 mg/L developed in 0.9% of the group receiving prescription ibuprofen. There was no significant difference in the incidence of renal impairment between acetaminophen and ibuprofen users except in those  $\geq 65$  years of age (relative risk = 1.3 in ibuprofen users, 95% C.I. = 1.1-1.7).

Radford conducted a retrospective chart review of the Mayo Clinic records for the years 1975-1995 to investigate the frequency of membranous nephropathy associated with NSAID use.<sup>69</sup> Of 125 patients identified with the early stages of this condition, the three that were taking ibuprofen had a duration of use from one to nine months, which far exceeds the recommended duration of OTC use.

Pospishil studied the renal biopsies of previously normal patients who developed renal complications after treatment with NSAIDs including OTC ibuprofen.<sup>70</sup> While information on dosages was not provided, the authors noted that the patients who developed renal symptoms had, in general, used NSAIDs for prolonged periods of time, ranging from 3 months to seven years.

#### **Safety Surveillance Data**

As mentioned previously, data from FDA's spontaneous reporting system for all single ingredient ibuprofen products from the period May 1984 through March 2002 have been reviewed. The data presented here include only the reports of adverse events associated with the administration of ibuprofen for ten days or less, at doses of 1200 mg/day or less, and in subjects 12 years of age or older, with no use of concomitant drugs reported (reports where any information was missing were also included). Note: The data that was included in the Agency's review of ibuprofen renal safety surveillance data (provided to the public on August 23, 2002) included reports submitted to FDA from May 1984 through August 9, 1999.

Of a total of 768 serious adverse event reports received in the last 18 years of post marketing surveillance for OTC ibuprofen, 93 contained at least one adverse event term related to the urogenital system. Of these, there were 26 reports of renal failure. This represents less than two cases reported each year during the OTC availability of ibuprofen, an extremely low reporting frequency that supports the adequacy of the current labeling. Additionally, none of these renal events resulted in death during this time period.

When data including those who took concomitant medication were examined, there were 10 deaths involving renal failure, seven females and three males. Six of the individuals were  $\geq 68$  years of age, and six were taking at least three other medications (in addition to ibuprofen), at the time of death. Given the limited amount of information available, it is not clear whether renal failure was a pre-treatment event, whether it was related to taking the other medications, related to another medical condition, or related to taking ibuprofen.

### **C. Safety in Overdose**

At the time ibuprofen was approved for OTC use, it was generally recognized that it posed significantly less risk than either acetaminophen or aspirin with respect to overdose. As is evident by data collected and reported by the American Association of Poison Control Centers (AAPCC) from 1987 through 2000, this continues to be the case. Ibuprofen exposures have resulted in the less severe outcomes, and fewer deaths, compared to aspirin and acetaminophen. During this timeframe, there have been only 49 fatalities from 528,396 reports of ibuprofen overdose (a rate of 0.009%), compared to 769 fatalities resulting from 978,014 reports of acetaminophen overdose (a rate of 0.079%) and 576 fatalities resulting from 221,356 reports of aspirin overdose (a rate of 0.26%).

### **IV. Development of Labeling for OTC Ibuprofen**

As previously mentioned, the labeling for all prescription NSAIDs includes detailed warnings about GI and renal toxicity. As the risk of these toxicities is dependent upon the drug, dose, and duration of use, ibuprofen was switched from prescription to OTC status based on:

- its favorable safety profile at prescription doses;

- the proposed maximum daily OTC dose of 1200 mg per day was less than one half of the approved maximum daily prescription dose (3200 mg), which was expected to pose minimal risks to consumers;
- the approved single dose of 200-400 mg was shown to a very effective analgesic and was designed to allow for flexibility in dosing where necessary

While drugs that are granted OTC status are felt to pose minimal safety risks to consumers, no drug is entirely safe. Therefore, the labeling for OTC drugs should clearly communicate the intended target population, indications for treatment, dosing instructions, populations at risk, potential harmful outcomes, and what to do should there be a harmful outcome. At the same time, labels should not be so overloaded with information as to dilute the information consumers need to read.

Labeling for prescription products (including NSAIDs) is lengthy and very detailed because it is primarily designed to provide the physician or learned intermediary with as much information as possible about the drug so that he/she can select the appropriate drug and provide appropriate counsel the patient. On the other hand, labeling for OTC products is intended for the consumer. The current labeling for OTC ibuprofen is based on data from a study designed by FDA. During the approval process, there was lengthy consideration by the Agency of whether potential consumer confusion and associated problems might occur with the introduction of this entirely new OTC analgesic. FDA took the unusual step of forming a multi-disciplinary internal task force to advise on the development of labeling for OTC ibuprofen. During the group's deliberations, it became evident that there were divergent views about how to most effectively communicate the warnings and precautions to consumers. Two different labels were developed reflecting the disparate views of the task force. One version was more general and indicated in broad terms when a consumer should consult a physician. The second version was more specific and listed nearly all the diseases and conditions that would require a user to consult a physician before use. Following a protocol developed by the Agency, the labels were tested in a mall intercept study involving 300 consumers from 13 locations throughout the US.

Results of the study were discussed in the Medical Officer's Review for the sponsor NDAs. Interestingly, many of the more general warning statements were better understood by consumers than the more specific ones. Subjects receiving the more specific label were more likely to self-diagnose their medical condition and determine the suitability for using ibuprofen without consulting a physician. However, those seeing the more general version were more likely to consult their doctor as a source of information about using the product rather than make a decision about taking the drug on their own. Based on the results of the research, the task force arrived at labeling they believed combined the better portions of each of the versions. As agreed to with the Agency, Sponsors provided educational campaigns for consumers and health professionals to make sure that aspirin sensitive individuals were suitably informed about OTC ibuprofen. Sponsors also worked with the Agency to create educational materials to promote safe and effective use of OTC ibuprofen.

Over the past 18 years, the labeling for OTC ibuprofen has been revised to include several new warnings. In 1986 when generic ibuprofen products came on the market, a warning was added to state clearly that the product should not be used with any other ibuprofen-containing product. In 1990, the Agency required sponsors to capitalize the statement "IF YOU EXPERIENCE ANY SYMPTOMS WHICH ARE UNUSUAL OR SEEM UNRELATED TO THE CONDITION FOR WHICH YOU TOOK IBUPROFEN CONSULT A DOCTOR BEFORE TAKING ANY MORE OF IT." This was implemented as a precautionary step by the Agency and, to the best of WCH's knowledge, was not in response to a specific incident or complaints from health care professionals.

In 1998, the Agency amended its regulations to require a revised allergy warning for NSAID drug products. OTC ibuprofen had included a warning for "ASPIRIN SENSITIVE PATIENTS" since the time of approval in 1984. Under the new regulation, this warning was replaced with the following:

**Allergy alert:** ibuprofen may cause a severe allergic reaction which may include:

- hives
- facial swelling
- asthma (wheezing)
- shock

**Do not use** if you have ever had an allergic reaction to any other pain reliever/fever reducer.

**Stop use and ask a doctor if** an allergic reaction occurs. Seek medical help right away.

Additionally, in 1998, the Agency issued a regulation requiring an organ specific alcohol warning on all OTC analgesic products. The following warning was added to OTC ibuprofen labeling:

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

In May 2002, the drug facts rulemaking became effective for many OTC drug products. This rulemaking requires a bulleted format and a standard order or presentation of information on the label for all OTC products. Wyeth Consumer Healthcare has revised Advil labeling to the required format. The "Warnings" and "Directions for Use" sections of the current label are presented below, and include specific statements that aid the consumer in using the product safely.

**Warnings**

**Allergy alert:** Ibuprofen may cause a severe allergic reaction which may include:

- hives
- facial swelling
- asthma (wheezing)
- shock

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

**Do not use** if you have ever had an allergic reaction to any other pain reliever/fever reducer

**Ask a doctor before use if you have**

- had problems or side effects with any pain reliever/fever reducer
- stomach pain

**Ask a doctor or pharmacist before use if you are**

- under a doctor's care for any continuing medical condition
- taking other drugs on a regular basis
- taking another product containing ibuprofen, or any other pain reliever/fever reducer

**When using this product take with food or milk if stomach upset occurs**

**Stop use and ask a doctor if**

- an allergic reaction occurs. Seek medical help right away.
- fever gets worse or lasts more than 3 days
- pain gets worse or lasts more than 10 days
- stomach pain occurs with the use of this product
- the painful area is red or swollen
- any new or unexpected symptoms occur

**If pregnant or breast-feeding,** ask a health professional before use. It is especially important not to use ibuprofen 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**

- do not take more than directed
- adults: take 1 tablet every 4 to 6 hours while symptoms occur
- if pain or fever does not respond to 1 tablet, 2 tablets may be used, but do not exceed 6 tablets in 24 hours, unless directed by a doctor
- the smallest effective dose should be used
- children: do not give to children under 12 unless directed by a doctor

As previously mentioned, on August 21, 2002, the Agency published a proposal in the Federal Register to amend the tentative final monograph (TFM) for OTC internal analgesic, antipyretic and antirheumatic drugs to include ibuprofen as a generally recognized safe and effective analgesic/antipyretic for OTC use. The Agency based its recommendation on the very favorable safety profile of OTC ibuprofen. Importantly, this safety profile has been generated from ibuprofen's current OTC label. As part of their proposal however, the Agency has recommended the addition of more specific GI and renal warnings to the label as follows:

### **Warnings**

**Allergy alert:** Ibuprofen may cause a severe allergic reaction which may include:

- hives
- facial swelling
- asthma (wheezing)
- shock

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

**Do not use** if you have ever had an allergic reaction to any other pain reliever/fever reducer

**Ask a doctor before use if you have**

- had problems or serious side effects with any from taking pain relievers/ or fever reducers
- stomach pain problems that last or come back, such as heartburn, upset stomach, or pain
- ulcers
- bleeding problems
- high blood pressure, heart or kidney disease, are taking a diuretic, or are over 65 years of age

**Ask a doctor or pharmacist before use if you are**

- under a doctor's care for any continuing medical any serious condition
- taking other drugs on a regular basis
- taking another any other product that containing ibuprofen, or any other pain reliever/fever reducer
- taking a prescription drug for anticoagulation (blood thinning)
- taking any other drug

**When using this product** take with food or milk if stomach upset occurs

**Stop use and ask a doctor if**

- an allergic reaction occurs. Seek medical help right away.
- pain gets worse or lasts more than 10 days
- fever gets worse or lasts more than 3 days
- stomach pain gets worse or lasts occurs with the use of this product
- redness or swelling is present in the painful area is red or swollen
- any new or unexpected symptoms appear occur

**If pregnant or breast-feeding,** ask a health professional before use. It is especially important not to use ibuprofen 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**

- **do not take more than directed**
- adults and children 12 years and over: take 1 tablet every 4 to 6 hours while symptoms occur persist
- if pain or fever does not respond to 1 tablet, 2 tablets may be used, but do not
- do not exceed 6 tablets in 24 hours, unless directed by a doctor
- the smallest effective dose should be used
- children under 12 years: ask a doctor do not give to children under 12 unless directed by a doctor

WCH looks forward to working with the Agency to evaluate the current, as well as alternate proposals for improving the label. As with the label comprehension study conducted in 1983 prior to the approval of OTC ibuprofen, greater specificity in the warnings statements may not prove to be as effective as the current more general warnings.

#### **V. Consumer Use Data**

As previously mentioned, WCH believes its labeling for OTC ibuprofen has been effective in communicating the appropriate use of this product. In addition to the very favorable safety profile that has been generated since it became available OTC, this is also supported by the following consumer use data which shows that few consumers exceed recommended doses.

In an Attitude and Usage study conducted over a 10-day period in 1996:<sup>71</sup>

- the average number of tablets taken per dose was approximately 2
- consumers took  $\geq 3$  tablets 11% of the time
- the average number of tablets taken per day was 3.6 (~720 mg)
- more than 6 tablets per day (>1200 mg) were taken only 8% of the time.

In a 30-day actual use study conducted in 3094 individuals with a history of using OTC analgesics who were provided with sufficient study medication for 10 days (60 pills):<sup>72</sup>

- 1.23% took more than 2 ibuprofen tablets per dose
- 7.5% took more than 6 ibuprofen tablets in 24 hours
- 3.72% took ibuprofen for more than 10 days for pain or for more than 3 days for fever

Data from a 2002 Gallup survey indicate that consumers of OTC ibuprofen use an average of 17.1 pills per month.<sup>73</sup>

- 36% use 1-4 pills/month
- 21% use 5-8 pills/month
- 30% use 9-29 pills/month
- 14% use  $\geq 30$  pills/month
  - 7.6% use 30- 50 pills/month
  - 4.1% use 51-100 pills/month

1.6% use 101-180 pills/month  
0.8% use > 180 pills/month

Survey data in 2002 indicate that about 65% of Advil's pill volume comes from those 18 to 49 years of age, and 10% from those 65 years or older. The major uses of the brand are: 34% for headache, 21% for arthritis pain, and 16% for muscle aches and pains.

## **VI. Conclusions**

Since ibuprofen's approval for OTC use in 1984, its safety profile has continued to be closely investigated, evaluated and assessed by WCH. While no drug, even if it is OTC, is completely safe, there is a vast amount of data indicating a very low risk of developing serious GI or renal toxicity when OTC ibuprofen is used according to the labeled dosing instructions (i.e. 200-400 mg every 4 – 6 hours, up to 1200 mg per day, for up to 10 days). Because it is critical that consumers follow the labeled dosing instructions for any drug, WCH has worked very closely with FDA in developing the current label for OTC ibuprofen. WCH believes that the long history of safe and effective use of OTC ibuprofen indicates that this labeling has been generally effective in communicating its appropriate use. We have presented consumer behavior data confirming that the vast majority of consumers follow the labeled instructions. While the Agency has recommended that ibuprofen be included in the Tentative Final Monograph, thereby recognizing it as being generally safe and effective, they have also proposed the addition of more specific GI and renal warnings to the label. Although WCH has not had sufficient time to consumer test or evaluate all of the proposed modifications, WCH is fully committed to working with the Agency on improving the label for all OTC analgesic products, including ibuprofen, where necessary. As in the past, WCH strongly believes that any proposed modifications to the label should be adequately tested to ensure the proposed changes actually benefit the consumer.

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**FINAL — CONFIDENTIAL**

**FINAL LABEL COMPREHENSION REPORT**

**TITLE:** Advil Analgesic Label Comprehension Study

**STUDY DESIGN:** In person label comprehension test in which 306 past six month Advil pain reliever users were interviewed. Respondents were exposed to the package label for the 100 count size Advil analgesic product.

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**STUDY DATES:** August 22 - August 29, 2002

**REPORT DATE:** October 24, 2002

## TABLE OF CONTENTS

<u>SECTION</u>	<u>PAGE</u>
I. INTRODUCTION -----	2
II. OBJECTIVES -----	2
III. ADMINISTRATIVE STRUCTURE -----	3
IV. STUDY DESIGN -----	4
V. MATERIALS AND METHODS -----	5
VI. STATISTICAL ANALYSIS -----	9
VII. RESULTS -----	11
A. Self Selection -----	11
a. What the Product Does -----	11
b. Self Selection -----	12
B. Scenarios for Selection/Deselection -----	15
a. Scenarios for Selection/Deselection Among Total Respondents and Age/Literacy Subgroups -----	15
b. Scenarios for Selection/Deselection Among Respondents Who Need to Consult a Physician and Those Claiming They Are Allergic to Pain Relievers/Fever Reducers -----	18
c. Pregnancy/Breast Feeding Warning -----	21
C. Dosing/Directions for Use -----	22
a. Directions for Use -----	22
b. Concomitant Use of Other Medications -----	23
D. When to Discontinue Use of Advil -----	24
E. Knowledge of Symptoms of Allergic Reaction to Ibuprofen -----	26
F. Package Readability -----	27
G. Physician Recommendation of Advil/Ibuprofen -----	28
a. Physician Recommendation of Advil -----	28
b. Patient Requests for Advil or Ibuprofen -----	28
c. Total Physician Recommendation/Patient Request for Advil -----	29
VIII. SUMMARY -----	30
IX. SUPPORTING TABLES -----	31

### APPENDICES

- A: Sample Distribution
- B: Interviewing Flow Chart
- C: Questionnaires
- D: The REALM Test
- E: Advil Carton Label
- F: Validation Report
- G: Curriculum Vitae of Morris S. Whitcup, Ph.D.
- H: Number of Interviews Completed in Each Interviewing Site
- I: Categorization of Correct and Incorrect Responses

## **I. INTRODUCTION**

Advil analgesic is indicated for the relief of minor aches and pains (due to headache, the common cold, toothache, muscular aches, backache, minor pain of arthritis, menstrual cramps) and for reducing fever.

Wyeth Consumer Healthcare has completed a label comprehension study (described in this report) to determine whether or not typical consumers comprehend the safe and proper use of this product according to the current carton label instructions for Advil analgesic tablets.

## **II. OBJECTIVES**

The communication objectives for this research were to determine whether or not typical consumers who have used Advil analgesic in the past six months comprehend the safe and proper use of this product according to carton label instructions relating to:

- Uses
- Warnings
- Directions

### III. ADMINISTRATIVE STRUCTURE

This study was designed, supervised and implemented by Advanced Analytics, Inc., under the direction of Morris S. Whitcup, Ph.D., President of Advanced Analytics, Inc., who also authored this report.

Biographical material about Dr. Whitcup is provided in Appendix G of this report.

Advanced Analytics, Inc., the contract research organization, was responsible for: preparation of all interviewing materials, including an interviewer's/supervisor's manual; contracting for and monitoring of interviewing; checking of all completed questionnaires for quality assurance purposes; validation; data entry and tabulation; and, with the assistance of Wyeth Consumer Healthcare, preparation of the final report.

#### IV. STUDY DESIGN

The subject population consisted of past six month Advil analgesic users (see below). Using the Screening Questionnaire (see Appendix C) potential respondents were classified as qualified or non-qualified to participate in the study. Quotas were assigned so that approximately half of those interviewed were 18 to 49 years of age and half were 50 years of age or older.

After being screened for qualification, qualified respondents were administered the Rapid Estimate of Adult Literacy in Medicine (REALM) in order to establish their literacy level. After completing the REALM, respondents were exposed to the carton label for Advil analgesic. Respondents were allowed as much time as desired to read the carton label; and, subsequently, the carton was left in view, so that the respondents could refer to the carton label as they wished during questioning.

Using the Main Questionnaire respondents were asked questions pertaining to self-selection, product warnings and directions for use.

At the end of the Main Questionnaire, limited demographic information (*i.e.*, race) and medical information was obtained.

The Main Questionnaire was developed based upon sound survey construction principles and practices. These included:

1. Asking questions in an unbiased and non-leading way.
2. Asking "open-ended" (volunteered response) questions pertaining to a topic before asking more specific questions.
3. Constructing "scenario" questions which demonstrate respondent ability to apply the material they had read.
4. Including "control" items in certain questions in order to minimize any potential "yea-saying" or "nay-saying" biases.

Interviewers were instructed to ask the questions exactly as worded. For open-ended questions, interviewers recorded respondent answers verbatim, clarifying any vague or general responses.

All completed questionnaires and terminated screening questionnaires were reviewed for adherence to study procedures. All data entry was 100% keypunch verified.

**V. MATERIALS AND METHODS****A. STUDY POPULATION****1. Inclusion Criteria**

Subjects were eligible for inclusion in the study provided they met the following criteria:

- a. Had to be age 18 or older at the time of screening,
- b. Completed a screening questionnaire,
- c. Had used Advil analgesic in the past six months preceding the interview.

Additionally, age quotas were established such that approximately one-fourth of the interviews were with subjects 18-34 years of age, one-fourth with subjects 35-49 years of age, and one-half with subjects 50 years of age or older.

A total of 306 interviews were conducted from August 22 - August 29, 2002 in 25 geographically dispersed interviewing sites:

**Northeast**

Boston, MA  
Hartford, CT  
Massapequa, NY  
Philadelphia, PA  
Rochester, NY  
Woodbridge, NJ

**South**

Baltimore, MD  
Ft. Lauderdale, FL  
Houston, TX  
Memphis, TN  
Nashville, TN  
New Orleans, LA

**Midwest**

Akron, OH  
Chicago, IL  
Cleveland, OH  
Detroit, MI  
Kansas City, KS  
Milwaukee, WI

**West**

Los Angeles, CA  
Phoenix, AZ  
San Diego, CA  
San Francisco, CA  
Santa Fe, NM  
Seattle, WA  
Tucson, AZ

The number of interviews completed in each of these 25 interviewing sites is shown in Appendix H.

## 2. Exclusion Criteria

Subjects were excluded from participating in the study if any of the following were noted:

- a. Were health care professionals, worked for a health care professional, or had immediate family members who were/worked for health care professionals or the Food and Drug Administration,
- b. Personally worked for or had immediate family members who were involved in the manufacture, wholesaling, retailing, or distribution of drugs or pharmaceutical products,
- c. Personally worked for or had immediate family members who worked for an advertising agency, market research company, package design company, TV or radio station or public relations company,
- d. Had been interviewed for a market research study in the previous 3 months, other than for a political poll,
- e. Indicated they were not comfortable being interviewed in English, or did not understand this question,
- f. Used eyeglasses or contact lenses for reading and did not have them available at the time of interview.

## B. RECRUITMENT PROCEDURES

The subjects were recruited utilizing shopping mall intercept screening.

### **C. STUDY INSTRUMENTS**

The following study materials were utilized in this research:

- a. Carton labels for Advil analgesic tablets - 100 count size -- See Appendix E.
- b. Screening Questionnaire, which was used to classify respondents as qualified or non-qualified to participate in the study -- See Appendix C.
- c. REALM Test. Although literacy level was not a screening criteria, literacy level was assessed utilizing the Rapid Estimate of Adult Literacy in Medicine (REALM). Subjects scoring 60 or below on this test are at an 8<sup>th</sup> grade or less reading level -- See Appendix D.
- d. Main Questionnaire -- See Appendix C.

Based on responses to the Screening Questionnaire, qualifying respondents were administered the Main Questionnaire and REALM. If the required number of interviews had already been completed for the age/gender quota group for which the respondent qualified, the interview was terminated.

### **D. QUALITY ASSURANCE IN DATA COLLECTION**

This survey was conducted in accordance with or exceeding generally accepted procedures for conducting market research. Some specific quality control procedures included:

1. **Field Administration/Monitoring of the Study**
  - a. Only interviewers who were pre-approved by Advanced Analytics, Inc. were assigned to the study. Interviewers were required to have at least 6 months of prior mall interviewing experience to qualify as interviewers for this study.
  - b. Before beginning actual interviewing, each interviewer was required to attend a study briefing, performed several practice interviews, and was pre-approved to administer the REALM test.
  - c. A detailed supervisor/interviewer manual specific to this survey was utilized. Each interviewer and supervisor was required to know the contents of the manual before beginning actual interviewing.

- d. A briefing tape of the REALM Test was prepared. This tape included correct pronunciation of all words included in the REALM Test.
- e. Each interviewing site provided periodic reports detailing their progress on the study.

## **2. Data Handling and Verification Methods**

- a. Each questionnaire received was thoroughly checked to ensure that the respondent qualified for the study and that the questionnaire had been properly administered and filled out.
- b. Data were key-entered with 100% key-entry verification (i.e., double data entry).
- c. A computer program was written and run which checked each completed questionnaire in terms of permissible responses, adherence to skip patterns, completeness and logical consistency.
- d. To ensure accuracy, computer tabulations were thoroughly checked against raw data counts.
- e. Names of respondents who participated and provided their telephone numbers were given to an independent validation service. This service randomly selected respondents from each of the interviewing sites for re-contact, with the goal of recontacting at least 40% of the respondents who provided telephone numbers at each site. In total, across sites, 49% of the respondents who provided telephone numbers were actually recontacted. No discrepancies were reported (see Validation Report contained in Appendix F).

## **VI. STATISTICAL ANALYSIS**

Respondents' answers to comprehension questions were categorized as "correct" or "incorrect" on a question by question or sub-question by sub-question basis. For certain questions or sub-questions, respondent answers coded as "correct" were further subdivided into "preferred" and "acceptable" responses -- *See Appendix I for categorization scheme.*

The percents of "correct"/"incorrect" responses, and, as appropriate, "preferred" and "acceptable", were calculated for each question on an overall basis as well as by subgroup as appropriate. A "preferred" response is a response that is technically what the carton label or educational insert indicates. An "acceptable" response is a response that is not specifically indicated on the carton label or educational inset, but is valid. Several of the responses classified as "acceptable" (See Appendix I) may reflect consumer caution about using a medication without first consulting with a physician.

For example, in Q4.0, Scenario c. of the Main Questionnaire, it was asked whether or not it is OK for a person who had the common cold but it otherwise in good health to use this product or whether they need to ask a doctor first. If a respondent answered that it is OK for this person to use this product, the response was classified as "preferred". If a respondent answered the person should ask the doctor first, the response was classified as "acceptable," since asking a doctor is an appropriate response.

For questions which allowed respondents to provide multiple answers, respondents were classified as falling into one of the three following exclusive groups:

- a. "Total Correct" - gave one or more correct responses to the particular question and gave no incorrect responses
- b. "Total Incorrect" - gave one or more incorrect responses
- c. "Total Undetermined" - gave a response or responses that could neither be classified as correct nor incorrect. To fall into this group, respondents could not have given any response which was classified as "correct" or "incorrect."

In order to determine whether respondents had appropriately selected/deselected themselves for use of Advil analgesic, the self-selection question (Questions #2.0-3.0 of Main Questionnaire) was analyzed, taking into account respondents' medical condition, drug allergies and medication use, as indicated in Questions #9.0, 9.8, 10.0, 11.0, and 12.0 of Main Questionnaire.

Answers to these questions were used to determine whether or not respondents had appropriately selected/deselected themselves for using Advil analgesic (Questions #2.0-3.0 of Main Questionnaire).

Upper and Lower Bounds for "Total Correct" were computed at the 95% level of confidence using the "score" interval estimation method for binomial proportions (Agresti, Alan and Coull, Brent A., "Approximate is Better than 'Exact' for Interval Estimation of Binomial Proportions," *The American Statistician*, May, 1998, Vol. 52, No. 2, pp. 119-126).

The term "net" is utilized in helping to analyze the results of this research. A "net" is an unduplicated count of the number or percent of respondents who have one or more answers recorded within a specified range of answers. For example, when asked what the product does, a respondent might give three correct responses. The 'Correct' net line would count that respondent only once, while the individual mentions within the net line would include the respondent three times (corresponding to the three responses that he/she gave). Thus, the individual mentions contained within a net may add to more than the percentage reported for that net.

The responses for each of the comprehension questions are shown in "Supporting Tables" and discussed in the text of this report, with summary tables shown as appropriate.

## VII. RESULTS

Full results, including 95% confidence levels, both across and within subgroups, are included in the tables appended to this report. The following text summarizes the main results. These are based on the percentages in total and for each subgroup shown.

### A. SELF SELECTION

#### a. What the Product Does

*(See Summary Table Below)*

Without exception, all respondents cited one or more correct indicated uses for Advil. Most commonly mentioned uses are pain relief and being a fever reducer. Headaches are the most often mentioned specific type of pain relieved.

Only a small minority of respondents (0.7%) cited an incorrect use.

**SUMMARY TABLE A)a**  
**Percent Answering What This Product Does**

Question		% Answering Correctly		
		Total Sample	Age 50+	Low Literacy (REALM Score 0 - 60)
#	Description			
	(Base:)	(306)	(149)	(47)
		%	%	%
1.5	% Cited any correct response	100.0	100.0	100.0
	Major correct responses:			
	Pain reliever / relieves pain	81.0	81.2	76.6
	Fever reducer / reduces fever	63.1	65.1	61.7
	Mentioned specific type of pain (headaches, muscle aches, etc.)	57.8	58.4	59.6
	Relieves minor aches and pains	42.5	45.6	34.0
1.5	% Answered correctly only	99.3	98.7	97.9
1.5	% Answered incorrectly	0.7	1.3	2.1

*(See Table 1)*

**b. Self Selection**

*(See Summary Tables on Next Page)*

Based upon responses to medical-related questions (Questions # 9.0, 9.8, 10.0, 11.0, 12.0 and 13.0), the 306 total respondents were classified into three groups:

1. Those who are not contraindicated according to the carton label and who, according to the carton label, have no need to consult a physician or healthcare professional before using this product. (n=142)
2. Those who need to consult a physician or healthcare professional before using this product (n=138)
3. Those who are contraindicated; namely, claim they ever had an allergic reaction to another pain reliever/fever reducer (n=26)\*

Of the 142 respondents who are neither contraindicated nor need to consult, 95.1% gave a correct response. 81.7% said that the product was OK for them to use for pain or fever without consulting a physician (Q2.0). An additional 13.4% said they would consult a physician before use.

Of the 138 respondents who need to consult, 27.5% either said they need to ask a doctor first (21.7%) or should not use the product at all (5.8%). However, 71.7% indicated it was OK for them to use Advil without asking a physician.

Many of the respondents who indicated they would not consult a physician before use (but according to the carton label need to consult) have already spoken to a physician about Advil.

- Among those who said it was OK for them to use the product without physicians consultation (but according to the carton label need to consult) 68.7% of these respondents had Advil recommended for their use by a physician (Question #14.0 of the Main Questionnaire) and/or had asked a physician whether it was OK for them to take Advil and the physician had said it was OK (Question #14.3-14.4 of the Main Questionnaire).

\* National data indicate that at most 1% of adults have ever experienced a true allergic reaction to a pain relieve / fever reducer. It is hypothesized that many of the 26 respondents in the present study claiming to have had an allergic reaction to a pain reliever / fever reducer did not in actuality have such a reaction.

- Thus, in total, 76.8% of those respondents who would need to consult a physician before using Advil analgesic have either: (a) already received physician approval to use Advil/ibuprofen, (b) indicated they would ask a doctor first before using this product, or (c) would not use this product at all.

Self-selection among those respondents claiming that they had an allergic reaction to any pain reliever/fever reducer shows a similar pattern of results.

- Of the 26 respondents who claim to have had an allergic reaction (and thus are contraindicated according to the carton label), 26.9% either said they need to ask a doctor first (19.2%) or should not use the product at all (7.7%). However, 73.1% indicated it was OK for them to use Advil without asking a physician.
- Among those respondents who said it was OK for them to use the product without physician consultation, 68.4% had Advil recommended for their use by a physician (Question #14.0 of the Main Questionnaire) and/or had asked a physician whether it was OK for them to take Advil and the physician had said it was OK (Question #14.3-14.4 of the Main Questionnaire).
- Thus, in total, 76.9% of those respondents with a claimed allergy to a pain reliever / fever reducer have either: (a) already received physician approval to use Advil / ibuprofen, (b) indicated they would ask a doctor first before using this product, or (c) would not use this product at all.

**Summary Table A)b**  
**Summary Of Self Selection And Physician Consultation**  
**Among Those Who Need To Consult And Those Claiming To Have**  
**An Allergy To Any Pain Reliever / Fever Reducer**

Question		% Answering Correctly	
		Need To Consult	Claimed Allergy To Any Pain Reliever
#	Description		
	(Base:)	(138)	(26) <sup>c</sup>
		%	%
2.0/ 3.0/	1. Said need to ask doctor first before using Advil (Q3.0)	21.7	19.2
14.0/ 14.3/ 14.4	2. Said okay to use without asking (Q3.0) but doctor recommended Advil or doctor said okay to take Advil / Ibuprofen (Q14.0, 14.3, 14.4)	49.3	50.0
	3. Said Advil not appropriate (Q2.0)	5.8	7.7
	<b>Total % Summing Across 1, 2 and 3</b>	<b>76.8</b>	<b>76.9</b>

c = Caution: Small base

(See Tables 2-6)

**B. SCENARIOS FOR SELECTION/DESELECTION****a. Scenarios for Selection/  
Deselection Among Total Respondents and Age Literacy Subgroups**  
*(See Summary Table on next page)*

When probed on an aided basis, the vast majority of respondents (88.9% or higher) can correctly determine, based on the carton label, that the product is appropriate for the following types of people without the need for physician consultation:

**Correctly Answered the Product Is Appropriate For:**

- The person got a backache last night and they've treated their backache in the past with Advil
- The person has the common cold but otherwise is in good health
- The person has a toothache but otherwise feels fine
- The person is currently taking a non-prescription cream for an episode of athlete's foot

Furthermore, the large majority of respondents correctly answered that the following types of people need to consult with a physician before using the product or should not use the product at all (87.9% or higher).

**Correctly Answered that the  
Person Needs to Consult/Should Not Use the Product At All:**

- The person consumes three or more alcoholic drinks per day
- The person is under a doctor's care for an ulcer
- The last time the person took a pain reliever they developed stomach pain
- The person wants to give the product in this box to his nine year old daughter who has a headache
- The person previously had an allergic reaction to a pain reliever
- The person is allergic to ibuprofen.

Additionally, while not as high a correct response as to the other selection/ deselection scenarios, the majority of respondents (85.3%) correctly said that a person needs to consult a physician if they are currently taking a prescription medication for high blood pressure.

The responses of older individuals (50+ years of age) and low literacy respondents are not substantially different than those of total respondents.

**SUMMARY TABLE B)a)1**  
**Summary of Responses Among Total Respondents**  
**(Scenario List I)**

Question #	Description	% Answering			
		OK To Take Without Consulting	Not Okay To Take	Need To Ask Doctor First	Total Correct
		%	%	%	%
4.0a	The person got a backache last night and they've treated their backache in the past with Advil	92.5(P)	2.3(I)	5.2(A)	97.7
4.0b	The person consumes three or more alcoholic drinks per day	5.9(I)	66.0(A)	26.8(P)	92.8
4.0c	The person has the common cold but is otherwise in good health	91.8(P)	5.2(I)	2.9(A)	94.8
4.0d	The person previously had an allergic reaction to a pain reliever	2.9(I)	40.2(P)	55.6(A)	95.8
4.0e	The person is under a doctor's care for an ulcer	8.2(I)	22.2(A)	67.6(P)	89.9
4.0f	The person has a toothache but otherwise feels fine	91.2(P)	4.9(I)	3.6(A)	94.8
4.0g	The person is allergic to ibuprofen	1.6(I)	69.6(P)	28.8(A)	98.4
4.0h	The person is currently taking a prescription medication for high blood pressure	12.4(I)	20.9(A)	64.4(P)	85.3
4.0i	The person is currently taking a non-prescription cream for an episode of athlete's foot	74.2(P)	7.5(I)	14.7(A)	88.9
4.0j	The last time the person took a pain reliever they developed stomach pain	4.9(I)	38.6(A)	56.2(P)	94.8
4.0k	The person wants to give the product in this box to his nine year old daughter who has a headache	10.8(I)	52.9(A)	35.0(P)	87.9

(P) Preferred response (A) Acceptable response

(I) Incorrect response

(See Tables 7-17)

**SUMMARY TABLE B)a)2**  
**Percent Answering Correctly (Scenario List I)**

Question		% Answering Correctly		
#	Description	Total Sample	Age 50+	Low Literacy (Realm Score 0-60)
	(Base:)	(306)	(149)	(47)
		%	%	%
4.0a	The person got a backache last night and they've treated their backache in the past with Advil	97.7	97.3	97.9
4.0b	The person consumes three or more alcoholic drinks per day	92.8	93.3	91.5
4.0c	The person has the common cold but is otherwise in good health	94.8	97.3	91.5
4.0d	The person previously had an allergic reaction to a pain reliever	95.8	93.3	97.9
4.0e	The person is under a doctor's care for an ulcer	89.9	88.6	87.2
4.0f	The person has a toothache but otherwise feels fine	94.8	97.3	93.6
4.0g	The person is allergic to ibuprofen	98.4	98.0	100.0
4.0h	The person is currently taking a prescription medication for high blood pressure	85.3	79.9	80.9
4.0i	The person is currently taking a non-prescription cream for an episode of athlete's foot	88.9	87.2	85.1
4.0j	The last time the person took a pain reliever they developed stomach pain	94.8	97.3	93.6
4.0k	The person wants to give the product in this box to his nine year old daughter who has a headache	87.9	87.9	85.1

*(See Tables 7-17)*

**b. Selected Scenarios for Selection/Deselection  
Among Respondents Who Need to Consult a Physician  
and Those Claiming They Are Allergic to Pain Relievers/Fever Reducers  
(See Summary Tables on pages 18 and 19)**

In order to better assess comprehension levels relating to selection/deselection, specified scenarios from List #1 were analyzed among the following groups of respondents:

- Respondents who according to the carton label need to consult a physician before product use, but in response to Questions 2.0 and 3.0 indicated that they product is appropriate for them to use and that it is OK to use this product without first asking their doctor
- Respondents who claimed they previously had an allergic reaction to a pain reliever or fever reducer, but in response to Questions 2.0 and 3.0 indicated that they product is appropriate for them to use and that it is OK to use this product without first asking their doctor

This analysis reveals that the vast majority of these respondents do in fact correctly comprehend carton warnings.

Among those who according to the carton label need to consult with a physician but indicated they did not need to do so, 84.8% or higher correctly responded to the following scenarios (either by indicating the person needs to consult or should not use this product at all):

- The person is under a doctor's care for an ulcer
- The person is currently taking a prescription medication for high blood pressure
- The last time the person took a pain reliever they developed stomach pain
- The person consumes three or more alcoholic drinks per day

**SUMMARY TABLE B)b)1**

**Percent Answering Correctly Specified Scenarios Among Those Who Need To Consult A Physician But Said It Is Ok To Use This Product Without Consulting With A Physician**

	<b>Question</b>	<b>% Correctly Answering</b>
		<b>Need To Consult But Said OK To Use Without Asking Physician</b>
#	Description	%
4.0a	Scenario List I: The person consumes three or more alcoholic drinks per day	92.9
4.0e	Scenario List I: The person is under a doctor's care for an ulcer	88.9
4.0h	Scenario List I: The person is currently taking prescription medication for high blood pressure	84.8
4.0j	Scenario List I: The last time the person took a pain reliever they developed stomach pain	93.9

*(See Table 18)*

Among those who claimed they are allergic to pain relievers/fever reducers but said it is OK for them to use this product without consulting with a physician, 89.5% or higher correctly responded to the following scenarios (either by indicating the person needs to consult or should not use this product at all):

- The person is allergic to ibuprofen
- The person previously had an allergic reaction to a pain reliever
- The last time the person took a pain reliever they developed stomach pain

**SUMMARY TABLE B)b)2**  
**Percent Answering Correctly Specified Scenarios Among**  
**Those Claiming They Are Allergic To Pain Relievers/Fever Reducers But**  
**Said It Is Ok To Use This Product Without Consulting With A Physician**

	Question	% Correctly Answering
		Allergic To Pain Relievers/ Fever Reducers But Said OK To Use Without Consulting With A Physician
#	Description	%
4.0d	Scenario List I: The person previously had an allergic reaction to a pain reliever	100.0
4.0g	Scenario List I: The person is allergic to ibuprofen	89.5
4.0j	Scenario List I: The last time the person took a pain reliever they developed stomach pain	100.0

*(See Table 19)*

**c. Pregnancy/Breast Feeding Warning**  
*(See Summary Table below)*

The vast majority of respondents (90.5%) correctly answered that a woman who is pregnant or breast feeding needs to consult a physician or other healthcare professional before using this product.

Correct comprehension was particularly high among women (92.8%)

By contrast, in response to a control item, 84.3% of respondents (and 91.5% of women) correctly indicated that a woman who has menstrual cramps can use this product without first consulting with a physician.

**SUMMARY TABLE B)c**  
**Percent Answering Correctly**

#	Question Description (Base:)	% Answering Correctly		
		Total Sample	Low Literacy (Realm Score 0-60)	Women
		(306)	(47)	(153)
5.5	Whether OK/not OK for woman who is pregnant/breast feeding to use this product without consulting with physician/healthcare professional	% 90.5	% 87.2	% 92.8
5.4	Whether women who has menstrual cramps can take product without consulting with a physician (Control item) - Total Correct	92.8	87.2	96.1
	Total Preferred - woman does not need to consult	84.3	80.9	91.5

*(See Tables 20- 21)*

**C. Dosing/Directions for Use**

**a. Directions for Use**

*(See Summary Table Below)*

Directions for use are clearly understood by respondents.

The vast majority of respondents correctly understood that the a person:

- Should take one or two tablets as an initial dose of this product (98%)
- Can take a maximum one to two tablets within a four to six hour period (88.2%)
- Can take a maximum of six tablets within a 24 hour period (96.4%)

It should be noted that the cited correct comprehension of dosing for the four to six hour period (88.2%) is actually a conservative figure. Depending upon spacing of doses, a person can actually take four tablets within a six hour period according to the range of four to six hours specified in the carton label and the maximum of two tablets per dose.

**SUMMARY TABLE C)a  
Percent Answering Correctly**

#	Question Description (Base:)	% Answering Correctly		
		Total Sample	Age 50+	Low Literacy (Realm Score 0-60)
		(306)	(149)	(47)
		%	%	%
7.0	Number of tablets should initially take	98.0	98.7	100.0
7.1	Maximum number of tablets can take within four to six hour period	88.2	86.6	83.0
7.3	Maximum number of tablets can take within twenty-four hour period	96.4	97.3	100.0

*(See Tables 22-24)*

**b. Concomitant Use of Other Medications**

*(See Summary Table Below)*

Warnings concerning not to take Advil concomitantly with other pain relievers or products containing pain relievers are moderately well understood.

The majority of respondents (77.8% or higher) do correctly understand that one should not take Advil:

- Along with another product containing ibuprofen
- Along with a tablet of another pain reliever such as Tylenol
- When also taking a multi-symptom cold or flu medication containing a pain reliever

Notably, older respondents (50+ years of age) and those scoring at 8<sup>th</sup> grade or lower on the REALM test (score of 60 or less) evidence average levels of correct comprehension of appropriateness of taking Advil concomitantly with other pain relievers or pain-reliever containing products.

**SUMMARY TABLE C)b**  
**Percent Answering Correctly**

#	Question Description (Base:)	% Answering Correctly		
		Total Sample (306) %	Age 50+ (149) %	Low Literacy (Realm Score 0-60) (47) %
5.0	Whether OK to take Advil along with another product containing ibuprofen	85.6	87.9	83.0
5.1	Whether OK to take Advil along with a tablet of another pain reliever such as Tylenol	78.8	78.5	72.3
5.3	Whether OK to take Advil when also taking a multi-symptoms cold or flu medication containing a pain reliever	77.8	78.5	72.3
5.2	Whether OK to take Advil when also taking a vitamin pill (control item) - Total correct	96.4	97.3	91.5
	Total preferred (OK to take without consulting)	81.0	87.9	83.0

*(See Tables 25-28)*

**D. WHEN TO DISCONTINUE USE OF ADVIL**

*(See Summary Table on Next Page)*

Directions relating to when to discontinue use of Advil are generally very well understood by respondents.

The vast majority of respondents (83.0% - 98.4%) correctly comprehended that one should discontinue use of Advil and see a doctor if:

- The person develops an allergic reaction to the product
- The person develops stomach pain after using the product
- The person took this product for a leg injury which now has become red and swollen
- The person took this product last night for a fever which today has become worse
- The person developed new or unexpected symptoms after using this product
- The person took this product for a fever for three days and still has a fever
- The person feels he/she needs to take this product for more than 10 days

The majority of respondents (70.6%-92.2%) also correctly understood that it is OK to use/continue using the product if:

- After taking one dose of this product the person's muscle ache got somewhat better
- The person starts using a non-prescription antibiotic cream for a few days for a minor wound
- The person started using this product last night and their toothache pain subsided somewhat
- The person has arthritis pain which they want to treat for three or four days

**SUMMARY TABLE D**  
**Percent Answering Correctly (Scenario List II)**

#	Question Description (Base:)	% Answering Correctly		
		Total Sample (306) %	Age 50+ (149) %	Low Literacy (Realm Score 0-60) (47) %
6.0a	The person develops an allergic reaction to this product*	97.1	98.0	95.7
6.0b	After taking the one dose of this product the person's muscle ache got somewhat better	92.2	90.6	89.4
6.0c	The person feels he / she needs to take this product for more than ten days*	83.0	78.5	78.7
6.0d	The person develops stomach pain after using this product*	97.7	99.3	93.6
6.0e	The person took this product for a leg injury which now has become red and swollen*	94.1	98.0	95.7
6.0f	The person starts using a non-prescription antibiotic cream for a few days for a minor wound	70.6	67.1	48.9
6.0g	The person started using this product last night and their toothache pain subsided somewhat	89.2	89.9	83.0
6.0h	The person took this product last night for a fever which today has become worse*	86.9	88.6	85.1
6.0i	The person developed new or unexpected symptoms after using this product*	98.4	100.0	97.9
6.0j	The person took this product for a fever for three days and still has a fever*	95.1	97.3	91.5
6.0k	The person has arthritis pain which they want to treat for three or four days	78.4	77.2	78.7

\* Label indicates that consumer should discontinue use of the product and consult a physician.

(See Tables 29-39)

**E. KNOWLEDGE OF SYMPTOMS OF ALLERGIC REACTION TO IBUPROFEN**

The vast majority of total respondents (89.2%) could correctly name (without prompting) one or more symptoms that are indicative of an allergic reaction to ibuprofen.

Hives is the symptom most apt to be cited by total respondents (82.0%), followed by facial swelling (72.2%) and asthma or wheezing (67.0%).

*(See Table 40)*

**F. PACKAGE READABILITY**

The majority of total respondents (75.5%) found the size of the print on the back of the package easy or very easy to see. An additional 19.6% indicated they had to strain but could see the print. Few (4.9%) said they could make out just a little bit of the print or could not make out the print at all.

*(See Table 41)*

## **G. PHYSICIAN RECOMMENDATION OF ADVIL/IBUPROFEN**

### **a. Physician Recommendation of Advil**

Somewhat under half of total respondents (45.8%) indicated that their doctor has ever recommended they take Advil.

- Almost half (49.3%) the respondents who according to the carton label need to consult a physician before using the product and half of those who claim they are allergic to a pain reliever/fever reducer (50.0%) said their doctor has ever recommended Advil.

*(See Tables 42-43)*

Among those respondents whose doctors recommended they take Advil, most report that their doctor told them to take one (21.4%) or two tablets (47.1) tablets per dose.

*(See Table 44)*

Many respondents (34.3% of those whose physicians recommended Advil) reported that their physician recommended that they take Advil for as long as needed. Physician instructions to taking Advil for a few days (11.4%), for two (10.7%) and three days (7.1%) are also commonly reported.

*(See Table 45)*

### **b. Patient Requests for Advil or Ibuprofen**

Approximately 40% of total respondents (39.5%) report that they have asked a doctor whether it was Ok for them to take Advil or another pain reliever or fever reducer that contains ibuprofen. In the vast majority of these cases (93.4%) the physician said it was OK for them to take it.

*(See Tables 46-49)*

**c. Total Physician Recommendation/Patient Request for Advil**

Almost 60% of total respondents (59.5%) indicate that their physician has either recommended they take Advil or when asked, their physician had indicated it was OK for them to take Advil/ibuprofen.

- Approximately two in three respondents who according to the carton label need to consult a physician before using Advil (64.5%) or claim they are allergic to pain relievers (69.2%) report that their physician has recommended that take Advil or it was OK for them to take Advil/ibuprofen.

*(See Tables 50-51)*

## VIII. SUMMARY

The Advil analgesic label is an effective vehicle for communicating product uses, warnings and correct dosage.

After reading the product label, the vast majority of respondents (85% or higher) correctly comprehend:

- What the product does
- Who should use it
- Who should not use it
- Who needs to consult with a physician or other healthcare professional before using this product
- When to discontinue use of the product
- What are the signs of an allergic reaction to ibuprofen
- Correct dosing of Advil analgesic (i.e., how many tablets to initially take and maximum dosage within four to six-hour and 24-hour periods).

There is moderately good communication (75% correct comprehension or higher) regarding proscribed concomitant use of medications (i.e., that Advil analgesic tablets should not be taken with other analgesics, with other products containing ibuprofen nor with multi-symptom cold or flu medications without prior physician consultation).

To a large degree low literacy respondents (8<sup>th</sup> grade or less literacy as determined by the REALM) and older individuals (those 50+ years of age) show comparable correct understanding of the label, as does the total sample.

The majority of the Advil users interviewed for this study (60%) have talked to their physician about the use of Advil/ibuprofen; their physician has either recommended that they take Advil or okayed their use of Advil/ibuprofen.

Consumers who are okay to use the product without consultation/are not contraindicated, overwhelmingly say it is okay for them to use Advil without physician consultation. The majority of consumers (76%-77%) who according to their medical condition should consult a physician before product use said they either:

- Would ask a physician before using Advil analgesic tablets
- Have previously consulted a physician who recommended Advil/said it was okay for them to use Advil/ibuprofen
- Would not use this product at all

**IX. SUPPORTING TABLES**

# SELF SELECTION

**Table 1**  
**WHAT ADVIL DOES ACCORDING TO PACKAGE (UNAIDED)**

	<u>Total</u>	<u>Age</u>			<u>Realm Score</u>	
		<u>18-34</u>	<u>35-49</u>	<u>50+</u>	<u>00-60</u>	<u>61-66</u>
Base: Total Respondents	(306)	(80)	(77)	(149)	(47)	(258)
	%	%	%	%	%	%
		(A)	(B)	(C)	(D)	(E)
<b><u>Correct (Net)</u></b>	<b><u>100.0</u></b>	<b><u>100.0</u></b>	<b><u>100.0</u></b>	<b><u>100.0</u></b>	<b><u>100.0</u></b>	<b><u>100.0</u></b>
Pain reliever / relieves pain	81.0	78.8	83.1	81.2	76.6	82.2
Fever reducer / reduces fever	63.1	66.3	55.8	65.1	61.7	63.2
<b><u>Specific type of pain / aches mentioned</u></b>	<b><u>57.8</u></b>	<b><u>62.5</u></b>	<b><u>51.9</u></b>	<b><u>58.4</u></b>	<b><u>59.6</u></b>	<b><u>57.4</u></b>
Headaches	50.3	55.0	42.9	51.7	53.2	49.6
Muscle aches	39.2	35.0	35.1	43.6	34.0	40.3
Minor pain of arthritis	37.6	41.3B	26.0	41.6B	36.2	37.6
Backaches	36.3	40.0	32.5	36.2	31.9	37.2
Toothache	35.3	37.5	31.2	36.2	31.9	35.7
Common cold	34.0	40.0B	24.7	35.6	31.9	34.1
Menstrual cramps	32.4	37.5	32.5	29.5	31.9	32.2
Relieves minor aches and pains	42.5	43.8	35.1	45.6	34.0	43.8
Reduces inflammation	1.0	1.3	-	1.3	2.1	0.8
<b><u>Undetermined (Net)</u></b>	<b><u>0.7</u></b>	<b><u>1.3</u></b>	<b><u>-</u></b>	<b><u>0.7</u></b>	<b><u>2.1</u></b>	<b><u>0.4</u></b>
Alcohol warning	0.3	-	-	0.7	2.1E	-
Sinus	0.3	1.3	-	-	-	0.4
Allergy	0.3	1.3	-	-	-	0.4
<b><u>Incorrect (Net)</u></b>	<b><u>0.7</u></b>	<b><u>-</u></b>	<b><u>-</u></b>	<b><u>1.3</u></b>	<b><u>2.1</u></b>	<b><u>0.4</u></b>
Asthma	0.3	-	-	0.7	2.1E	-
Helps you relax / takes anxiety away	0.3	-	-	0.7	-	0.4
<b>Correct Only</b>	<b>99.3</b>	<b>100.0</b>	<b>100.0</b>	<b>98.7</b>	<b>97.9</b>	<b>99.6</b>
<b><u>Confidence Intervals</u></b>						
Lower Bound	.9758	.9542	.9525	.9530	.8893	.9782
Upper Bound	.9980	1.00	1.00	.9965	.9963	.9993

ABCDE = Significantly higher than indicated cell at the 95% level of confidence.

Q1.5 According to what the package says, what does this product do? Please feel free to refer to the package if you wish.

Table 2

WHETHER ADVIL IS APPROPRIATE FOR RESPONDENT  
TO USE FOR PAIN OR FEVER ACCORDING TO PACKAGE

	<u>No Need to Consult</u> (142) %
Base: Total Respondents	
<u>Yes</u>	<u>95.1</u>
Okay to use without asking (preferred)	81.7
Need to ask doctor first (acceptable)	13.4
Don't know (incorrect)	-
No (incorrect)	4.9
<u>Total Correct</u>	<u>95.1</u>
Preferred	81.7
Acceptable	13.4
Total incorrect	4.9
<u>Confidence Intervals</u>	
Lower Bound	.9021
Upper Bound	.9761

**Q2.0** According to the information on this package (*point to package*) and thinking specifically about your own current medical situation today, as well as your medical history, is this product an appropriate product for you to use if you had pain or fever?

**Q3.0** According to the package information, is it OK for you to use this product without first asking your doctor, or do you need to ask your doctor first before using this product?

Table 3

WHETHER ADVIL IS APPROPRIATE FOR RESPONDENT  
TO USE FOR PAIN OR FEVER ACCORDING TO PACKAGE

Base: Total Respondents	<u>Need to Consult</u> (138) %
<u>Yes</u>	<u>94.2</u>
Okay to use without asking (incorrect)	71.7
Need to ask doctor first (preferred)	21.7
Don't know (incorrect)	0.7
No (acceptable)	5.8
 <u>Total Correct</u>	 <u>27.5</u>
Preferred	21.7
Acceptable	5.8
Total incorrect	72.4
 <u>Confidence Intervals</u>	
Lower Bound	.2074
Upper Bound	.3548

- Q2.0** According to the information on this package (*point to package*) and thinking specifically about your own current medical situation today, as well as your medical history, is this product an appropriate product for you to use if you had pain or fever?
- Q3.0** According to the package information, is it OK for you to use this product without first asking your doctor, or do you need to ask your doctor first before using this product?

Table 4

WHETHER ADVIL IS APPROPRIATE FOR RESPONDENT  
TO USE FOR PAIN OR FEVER ACCORDING TO PACKAGE

Base: Total Respondents	<u>Allergic to Pain Relievers</u> (26) <sup>c</sup> %
<u>Yes</u>	<u>92.3</u>
Okay to use without asking (incorrect)	73.1
Need to ask doctor first (acceptable)	19.2
Don't know (incorrect)	-
No (preferred)	7.7
<u>Total Correct</u>	<u>26.9</u>
Preferred	7.7
Acceptable	19.2
Total incorrect	73.1
<u>Confidence Intervals</u>	
Lower Bound	.1369
Upper Bound	.4606

<sup>c</sup> Caution: Small base

- Q2.0 According to the information on this package (*point to package*) and thinking specifically about your own current medical situation today, as well as your medical history, is this product an appropriate product for you to use if you had pain or fever?
- Q3.0 According to the package information, is it OK for you to use this product without first asking your doctor, or do you need to ask your doctor first before using this product?

Table 5

**PRIOR CONSULTATION ABOUT ADVIL AMONG RESPONDENTS  
WHO EITHER NEED TO CONSULT A PHYSICIAN BEFORE USING THE PRODUCT  
OR ARE CONTRAINDICATED AND WHO SAID  
IT WAS OK TO TAKE THE PRODUCT WITHOUT FIRST ASKING A PHYSICIAN**

Base: Total Respondents	<u>Need to Consult/ Said OK to Take</u> (99) %	<u>Claimed Allergy/ Said OK to Take</u> (19) <sup>c</sup> %
<b><u>Doctor Recommended/OK to Take (Net)</u></b>	<b><u>68.7</u></b>	<b><u>68.4</u></b>
Doctor recommended	51.5	47.4
Doctor said OK to take	40.4	47.4
<b><u>Confidence Intervals</u></b>		
Lower Bound	.5901	.4599
Upper Bound	.7699	.8462

<sup>c</sup> Caution: Small base

- Q2.0** According to the information on this package (*point to package*) and thinking specifically about your own current medical situation today, as well as your medical history, is this product an appropriate product for you to use if you had pain or fever?
- Q3.0** According to the package information, is it OK for you to use this product without first asking your doctor, or do you need to ask your doctor first before using this product?
- Q14.0** Has your doctor ever recommended that you take Advil?
- Q14.3** You may or may not have already mentioned this... Have you ever asked your doctor whether or not it was OK for you to take Advil or another non-prescription pain reliever or fever reducer that contains ibuprofen?
- Q14.4** The last time you asked your doctor about Advil or another non-prescription pain reliever or fever reducer that contains Ibuprofen, did the doctor say it was Ok for you to take that type of product or Not Okay for you to take that type of product?

Table 6

SUMMARY OF SELF SELECTION AND PHYSICIAN CONSULTATION  
AMONG SUBJECTS WHO NEED TO CONSULT  
ABOUT ADVIL OR ARE ALLERGIC TO ANALGESICS

	<u>Need to Consult</u> (138) %	<u>Claimed Allergy</u> (26) <sup>c</sup> %
Base: Total Respondents		
<u>Yes, Advil Appropriate</u>	<u>94.2</u>	<u>92.3</u>
<u>OK to Use Without Asking</u>	<u>71.7</u>	<u>73.1</u>
Doctor recommended Advil or said OK to take (1)	49.3	50.0
Did not recommend/did not say OK to take/ don't know	22.5	23.1
Need to ask doctor first (2)	21.7	19.2
Don't know/not sure	0.7	-
<u>No, Not Appropriate (3)</u>	<u>5.8</u>	<u>7.7</u>
<b>Total (1), (2) and (3)</b>	<b>76.8</b>	<b>76.9</b>
<u>Confidence Interval</u>		
Lower Bound	.6909	.5792
Upper Bound	.8306	.8895

<sup>c</sup> Caution: Small base

- Q2.0** According to the information on this package (*point to package*) and thinking specifically about your own current medical situation today, as well as your medical history, is this product an appropriate product for you to use if you had pain or fever?
- Q3.0** According to the package information, is it OK for you to use this product without first asking your doctor, or do you need to ask your doctor first before using this product?
- Q14.0** Has your doctor ever recommended that you take Advil?
- Q14.3** You may or may not have already mentioned this... Have you ever asked your doctor whether or not it was OK for you to take Advil or another non-prescription pain reliever or fever reducer that contains ibuprofen?
- Q14.4** The last time you asked your doctor about Advil or another non-prescription pain reliever or fever reducer that contains Ibuprofen, did the doctor say it was Ok for you to take that type of product or Not Okay for you to take that type of product?

Table 7

**SCENARIO LIST I (AIDED): THE PERSON GOT A BACKACHE LAST NIGHT  
AND THEY'VE TREATED THEIR BACKACHE IN THE PAST WITH ADVIL**

	<u>Total</u>	<u>Age</u>			<u>Realm Score</u>	
		<u>18-34</u>	<u>35-49</u>	<u>50+</u>	<u>00-60</u>	<u>61-66</u>
Base: Total Respondents	(306)	(80)	(77)	(149)	(47)	(258)
	%	%	%	%	%	%
		(A)	(B)	(C)	(D)	(E)
Yes, okay (preferred)	92.5	88.8	92.2	94.6	89.4	93.0
No, not okay (incorrect)	2.3	2.5	1.3	2.7	2.1	2.3
Needs to ask a doctor first (acceptable)	5.2	8.8C	6.5	2.7	8.5	4.7
<b><u>Total Correct</u></b>	<b><u>97.7</u></b>	<b><u>97.5</u></b>	<b><u>98.7</u></b>	<b><u>97.3</u></b>	<b><u>97.9</u></b>	<b><u>97.7</u></b>
Preferred	92.5	88.8	92.2	94.6	89.4	93.0
Acceptable	5.2	8.8	6.5	2.7	8.5	4.7
Total incorrect	2.3	2.5	1.3	2.7	2.1	2.3
<b><u>Confidence Intervals</u></b>						
Lower Bound	.9534	.9134	.9300	.9328	.8893	.9505
Upper Bound	.9888	.9931	.9977	.9894	.9963	.9895

ABCDE = Significantly higher than indicated cell at the 95% level of confidence.

**Q4.0** We would like to better understand what the package says to people. Please think of adult men and women who have a minor ache or pain---such as headache, toothache or backache --- or fever. Imagine that one of these people asked you about this product (*point to product*). For each of these people I describe, please tell me whether, according to the package label, it's OK for this person to take this product, it's not okay for them to take this product or (*pause*) they need to ask a doctor first before taking this product.

The choices are listed on this card. (*Hand Card 4.0*)

Let's start with (*Read X'd Type Of Person*). According to the package, is it OK for this person to take this product, it's not okay for them to take this product, or they need to ask a doctor first?

Table 8

**SCENARIO LIST I (AIDED):**  
**THE PERSON CONSUMES THREE OR MORE ALCOHOLIC DRINKS PER DAY**

	<u>Total</u>	<u>Age</u>			<u>Realm Score</u>	
		<u>18-34</u>	<u>35-49</u>	<u>50+</u>	<u>00-60</u>	<u>61-66</u>
Base: Total Respondents	(306)	(80)	(77)	(149)	(47)	(258)
	%	%	%	%	%	%
		(A)	(B)	(C)	(D)	(E)
Yes, okay (incorrect)	5.9	2.5	10.4A	5.4	6.4	5.8
No, not okay (acceptable)	66.0	73.8B	58.4	65.8	78.7E	63.6
Needs to ask a doctor first (preferred)	26.8	22.5	29.9	27.5	12.8	29.5D
Don't know (incorrect)	1.3	1.3	1.3	1.3	2.1	1.2
<b><u>Total Correct</u></b>	<b><u>92.8</u></b>	<b><u>96.3</u></b>	<b><u>88.3</u></b>	<b><u>93.3</u></b>	<b><u>91.5</u></b>	<b><u>93.0</u></b>
Preferred	26.8	22.5	29.9	27.5	12.8	29.5
Acceptable	66.0	73.8	58.4	65.8	78.7	63.6
Total incorrect	7.2	3.8	11.7	6.7	8.5	7.0
<b><u>Confidence Intervals</u></b>						
Lower Bound	.8934	.8961	.7924	.8810	.8008	.8921
Upper Bound	.9520	.9874	.9372	.9632	.9665	.9552

ABCDE = Significantly higher than indicated cell at the 95% level of confidence.

**Q4.0** We would like to better understand what the package says to people. Please think of adult men and women who have a minor ache or pain---such as headache, toothache or backache --- or fever. Imagine that one of these people asked you about this product (*point to product*). For each of these people I describe, please tell me whether, according to the package label, it's OK for this person to take this product, it's not okay for them to take this product or (*pause*) they need to ask a doctor first before taking this product.

The choices are listed on this card. (*Hand Card 4.0*)

Let's start with (*Read X'd Type Of Person*). According to the package, is it OK for this person to take this product, it's not okay for them to take this product, or they need to ask a doctor first?

Table 9

**SCENARIO LIST I (AIDED):  
THE PERSON HAS THE COMMON COLD BUT IS OTHERWISE IN GOOD HEALTH**

	Total	Age			Realm Score	
		18-34	35-49	50+	00-60	61-66
Base: Total Respondents	(306)	(80)	(77)	(149)	(47)	(258)
	%	%	%	%	%	%
		(A)	(B)	(C)	(D)	(E)
Yes, okay (preferred)	91.8	90.0	87.0	95.3B	85.1	93.0
No, not okay (incorrect)	5.2	6.3	9.1C	2.7	8.5	4.7
Needs to ask a doctor first (acceptable)	2.9	3.8	3.9	2.0	6.4	2.3
<b><u>Total Correct</u></b>	<b><u>94.8</u></b>	<b><u>93.8</u></b>	<b><u>90.9</u></b>	<b><u>97.3</u></b>	<b><u>91.5</u></b>	<b><u>95.3</u></b>
Preferred	91.8	90.0	87.0	95.3	85.1	93.0
Acceptable	2.9	3.8	3.9	2.0	6.4	2.3
Total incorrect	5.2	6.3	9.1	2.7	8.5	4.7
<b><u>Confidence Intervals</u></b>						
Lower Bound	.9171	.8625	.8239	.9328	.8008	.9199
Upper Bound	.9678	.9733	.9552	.9894	.9665	.9728

ABCDE = Significantly higher than indicated cell at the 95% level of confidence.

**Q4.0** We would like to better understand what the package says to people. Please think of adult men and women who have a minor ache or pain—such as headache, toothache or backache — or fever. Imagine that one of these people asked you about this product (*point to product*). For each of these people I describe, please tell me whether, according to the package label, it's OK for this person to take this product, it's not okay for them to take this product or (*pause*) they need to ask a doctor first before taking this product.

The choices are listed on this card. (*Hand Card 4.0*)

Let's start with (*Read X'd Type Of Person*). According to the package, is it OK for this person to take this product, it's not okay for them to take this product, or they need to ask a doctor first?

Table 10

**SCENARIO LIST I (AIDED):**  
**THE PERSON PREVIOUSLY HAD AN ALLERGIC REACTION TO A PAIN RELIEVER**

	<u>Total</u>	<u>Age</u>			<u>Realm Score</u>	
		<u>18-34</u>	<u>35-49</u>	<u>50+</u>	<u>00-60</u>	<u>61-66</u>
Base: Total Respondents	(306)	(80)	(77)	(149)	(47)	(258)
	%	%	%	%	%	%
		(A)	(B)	(C)	(D)	(E)
Yes, okay (incorrect)	2.9	-	1.3	5.4A	2.1	3.1
No, not okay (preferred)	40.2	37.5	46.8	38.3	34.0	41.5
Needs to ask a doctor first (acceptable)	55.6	60.0	51.9	55.0	63.8	53.9
Don't know (incorrect)	1.3	2.5	-	1.3	-	1.6
<b><u>Total Correct</u></b>	<b><u>95.8</u></b>	<b><u>97.5</u></b>	<b><u>98.7</u></b>	<b><u>93.3</u></b>	<b><u>97.9</u></b>	<b><u>95.3</u></b>
Preferred	40.2	37.5	46.8	38.3	34.0	41.5
Acceptable	55.6	60.0	51.9	55.0	63.8	53.9
Total incorrect	4.2	2.5	1.3	6.7	2.1	4.7
<b><u>Confidence Intervals</u></b>						
Lower Bound	.9293	.9134	.9300	.8810	.8893	.9199
Upper Bound	.9754	.9931	.9977	.9632	.9963	.9728

ABCDE = Significantly higher than indicated cell at the 95% level of confidence.

**Q4.0** We would like to better understand what the package says to people. Please think of adult men and women who have a minor ache or pain—such as headache, toothache or backache — or fever. Imagine that one of these people asked you about this product (*point to product*). For each of these people I describe, please tell me whether, according to the package label, it's OK for this person to take this product, it's not okay for them to take this product or (*pause*) they need to ask a doctor first before taking this product.

The choices are listed on this card. (*Hand Card 4.0*)

Let's start with (*Read X'd Type Of Person*). According to the package, is it OK for this person to take this product, it's not okay for them to take this product, or they need to ask a doctor first?

Table 11

**SCENARIO LIST I (AIDED):**  
**THE PERSON IS UNDER A DOCTOR'S CARE FOR AN ULCER**

	<u>Total</u> (306) %	<u>Age</u>			<u>Realm Score</u>	
		<u>18-34</u> (80) % (A)	<u>35-49</u> (77) % (B)	<u>50+</u> (149) % (C)	<u>00-60</u> (47) % (D)	<u>61-66</u> (258) % (E)
Base: Total Respondents						
Yes, okay (incorrect)	8.2	5.0	13.0	7.4	12.8	7.4
No, not okay (acceptable)	22.2	21.3	24.7	21.5	25.5	21.7
Needs to ask a doctor first (preferred)	67.6	73.8	62.3	67.1	61.7	68.6
Don't know (incorrect)	2.0	-	-	4.0	-	2.3
<b><u>Total Correct</u></b>	<b><u>89.9</u></b>	<b><u>95.0</u></b>	<b><u>87.0</u></b>	<b><u>88.6</u></b>	<b><u>87.2</u></b>	<b><u>90.3</u></b>
Preferred	67.6	73.8	62.3	67.1	61.7	68.6
Acceptable	22.2	21.3	24.7	21.5	25.5	21.7
Total incorrect	10.2	5.0	13.0	11.4	12.8	9.7
<b><u>Confidence Intervals</u></b>						
Lower Bound	.8590	.8784	.7770	.8250	.7479	.8608
Upper Bound	.9271	.9804	.9278	.9276	.9399	.9334

ABCDE = Significantly higher than indicated cell at the 95% level of confidence.

**Q4.0** We would like to better understand what the package says to people. Please think of adult men and women who have a minor ache or pain—such as headache, toothache or backache — or fever. Imagine that one of these people asked you about this product (*point to product*). For each of these people I describe, please tell me whether, according to the package label, it's OK for this person to take this product, it's not okay for them to take this product or (*pause*) they need to ask a doctor first before taking this product.

The choices are listed on this card. (*Hand Card 4.0*)

Let's start with (*Read X'd Type Of Person*). According to the package, is it OK for this person to take this product, it's not okay for them to take this product, or they need to ask a doctor first?

Table 12

SCENARIO LIST I (AIDED):  
THE PERSON HAS A TOOTHACHE BUT OTHERWISE FEELS FINE

	Total	Age			Realm Score	
		18-34	35-49	50+	00-60	61-66
Base: Total Respondents	(306)	(80)	(77)	(149)	(47)	(258)
	%	%	%	%	%	%
		(A)	(B)	(C)	(D)	(E)
Yes, okay (preferred)	91.2	87.5	85.7	90.0AB	91.5	91.1
No, not okay (incorrect)	4.9	6.3	9.1C	2.0	6.4	4.7
Needs to ask a doctor first (acceptable)	3.6	6.3C	5.2	1.3	2.1	3.9
Don't know (incorrect)	0.3	-	-	0.7	-	0.4
<b><u>Total Correct</u></b>	<b><u>94.8</u></b>	<b><u>93.8</u></b>	<b><u>90.9</u></b>	<b><u>97.3</u></b>	<b><u>93.6</u></b>	<b><u>95.0</u></b>
Preferred	91.2	87.5	85.7	96.0	91.5	91.1
Acceptable	3.6	6.3	5.2	1.3	2.1	3.9
Total incorrect	5.2	6.3	9.1	2.7	6.4	5.1
<b><u>Confidence Intervals</u></b>						
Lower Bound	.9171	.8625	.8239	.9328	.8281	.9162
Upper Bound	.9678	.9733	.9552	.9894	.9780	.9706

ABCDE = Significantly higher than indicated cell at the 95% level of confidence.

**Q4.0** We would like to better understand what the package says to people. Please think of adult men and women who have a minor ache or pain—such as headache, toothache or backache --- or fever. Imagine that one of these people asked you about this product (*point to product*). For each of these people I describe, please tell me whether, according to the package label, it's OK for this person to take this product, it's not okay for them to take this product or (*pause*) they need to ask a doctor first before taking this product.

The choices are listed on this card. (*Hand Card 4.0*)

Let's start with (*Read X'd Type Of Person*). According to the package, is it OK for this person to take this product, it's not okay for them to take this product, or they need to ask a doctor first?

Table 13

SCENARIO LIST I (AIDED):  
THE PERSON IS ALLERGIC TO IBUPROFEN

	Total	Age			Realm Score	
		18-34	35-49	50+	00-60	61-66
Base: Total Respondents	(306)	(80)	(77)	(149)	(47)	(258)
	%	%	%	%	%	%
		(A)	(B)	(C)	(D)	(E)
Yes, okay (incorrect)	1.6	1.3	1.3	2.0	-	1.9
No, not okay (preferred)	69.6	68.8	72.7	68.5	59.6	71.3
Needs to ask a doctor first (acceptable)	28.8	30.0	26.0	29.5	40.4	26.7
<b><u>Total Correct</u></b>	<b><u>98.4</u></b>	<b><u>98.8</u></b>	<b><u>98.7</u></b>	<b><u>98.0</u></b>	<b><u>100.0</u></b>	<b><u>98.1</u></b>
Preferred	69.6	68.8	72.7	68.5	59.6	71.3
Acceptable	28.8	30.0	26.0	29.5	40.4	26.7
Total incorrect	1.6	1.3	1.3	2.0	-	1.9
<b><u>Confidence Intervals</u></b>						
Lower Bound	.9628	.9333	.9300	.9427	.9244	.9560
Upper Bound	.9932	.9979	.9977	.9932	1.00	.9919

ABCDE = Significantly higher than indicated cell at the 95% level of confidence.

**Q4.0** We would like to better understand what the package says to people. Please think of adult men and women who have a minor ache or pain—such as headache, toothache or backache — or fever. Imagine that one of these people asked you about this product (*point to product*). For each of these people I describe, please tell me whether, according to the package label, it's OK for this person to take this product, it's not okay for them to take this product or (*pause*) they need to ask a doctor first before taking this product.

The choices are listed on this card. (*Hand Card 4.0*)

Let's start with (*Read X'd Type Of Person*). According to the package, is it OK for this person to take this product, it's not okay for them to take this product, or they need to ask a doctor first?

Table 14

**SCENARIO LIST I (AIDED): THE PERSON IS  
CURRENTLY TAKING A PRESCRIPTION MEDICATION FOR HIGH BLOOD PRESSURE**

	Total	Age			Realm Score	
		18-34	35-49	50+	00-60	61-66
Base: Total Respondents	(306)	(80)	(77)	(149)	(47)	(258)
	%	%	%	%	%	%
		(A)	(B)	(C)	(D)	(E)
Yes, okay (incorrect)	12.4	5.0	10.4	17.4A	19.1	11.2
No, not okay (acceptable)	20.9	22.5	23.4	18.8	34.0E	18.6
Needs to ask a doctor first (preferred)	64.4	71.3	63.6	61.1	46.8	67.4D
Don't know (incorrect)	2.3	1.3	2.6	2.7	-	2.7
<b><u>Total Correct</u></b>	<b><u>85.3</u></b>	<b><u>93.8</u></b>	<b><u>87.0</u></b>	<b><u>79.9</u></b>	<b><u>80.9</u></b>	<b><u>86.0</u></b>
Preferred	64.4	71.3	63.6	61.1	46.8	67.4
Acceptable	20.9	22.5	23.4	18.8	34.0	18.6
Total incorrect	14.7	6.3	13.0	20.1	19.1	13.9
<b><u>Confidence Intervals</u></b>						
Lower Bound	.8090	.8625	.7770	.7275	.6751	.8124
Upper Bound	.8883	.9733	.9278	.8555	.8962	.8971

ABCDE = Significantly higher than indicated cell at the 95% level of confidence.

**Q4.0** We would like to better understand what the package says to people. Please think of adult men and women who have a minor ache or pain---such as headache, toothache or backache --- or fever. Imagine that one of these people asked you about this product (*point to product*). For each of these people I describe, please tell me whether, according to the package label, it's OK for this person to take this product, it's not okay for them to take this product or (*pause*) they need to ask a doctor first before taking this product.

The choices are listed on this card. (*Hand Card 4.0*)

Let's start with (*Read X'd Type Of Person*). According to the package, is it OK for this person to take this product, it's not okay for them to take this product, or they need to ask a doctor first?

Table 15

**SCENARIO LIST I (AIDED): THE PERSON IS CURRENTLY  
TAKING A NON-PRESCRIPTION CREAM FOR AN EPISODE OF ATHLETE'S FOOT**

	Total	Age			Realm Score	
		18-34	35-49	50+	00-60	61-66
Base: Total Respondents	(306)	(80)	(77)	(149)	(47)	(258)
	%	%	%	%	%	%
		(A)	(B)	(C)	(D)	(E)
Yes, okay (preferred)	74.2	63.8	84.4A	74.5	57.4	77.1D
No, not okay (incorrect)	7.5	7.5	6.5	8.1	14.9E	6.2
Needs to ask a doctor first (acceptable)	14.7	26.3BC	6.5	12.8	27.7E	12.4
Don't know (incorrect)	3.6	2.5	2.6	4.7	-	4.3
<b><u>Total Correct</u></b>	<b><u>88.9</u></b>	<b><u>90.0</u></b>	<b><u>90.9</u></b>	<b><u>87.2</u></b>	<b><u>85.1</u></b>	<b><u>89.5</u></b>
Preferred	74.2	63.8	84.4	74.5	57.4	77.1
Acceptable	14.7	26.3	6.5	12.8	27.7	12.4
Total incorrect	11.1	10.0	9.1	12.8	14.9	10.5
<b><u>Confidence Intervals</u></b>						
Lower Bound	.8489	.8149	.8239	.8089	.7231	.8516
Upper Bound	.9195	.9485	.9552	.9164	.9529	.9268

ABCDE = Significantly higher than indicated cell at the 95% level of confidence.

**Q4.0** We would like to better understand what the package says to people. Please think of adult men and women who have a minor ache or pain—such as headache, toothache or backache — or fever. Imagine that one of these people asked you about this product (*point to product*). For each of these people I describe, please tell me whether, according to the package label, it's OK for this person to take this product, it's not okay for them to take this product or (*pause*) they need to ask a doctor first before taking this product.

The choices are listed on this card. (*Hand Card 4.0*)

Let's start with (*Read X'd Type Of Person*). According to the package, is it OK for this person to take this product, it's not okay for them to take this product, or they need to ask a doctor first?

Table 16

**SCENARIO LIST I (AIDED): THE LAST TIME THE PERSON  
TOOK A PAIN RELIEVER THEY DEVELOPED STOMACH PAIN**

	<u>Total</u>	<u>Age</u>			<u>Realm Score</u>	
		<u>18-34</u>	<u>35-49</u>	<u>50+</u>	<u>00-60</u>	<u>61-66</u>
Base: Total Respondents	(306)	(80)	(77)	(149)	(47)	(258)
	%	%	%	%	%	%
		(A)	(B)	(C)	(D)	(E)
Yes, okay (incorrect)	4.9	7.5	6.5	2.7	6.4	4.7
No, not okay (acceptable)	38.6	41.3	37.7	37.6	42.6	38.0
Needs to ask a doctor first (preferred)	56.2	50.0	55.8	59.7	51.1	57.0
Don't know (incorrect)	0.3	1.3	-	-	-	0.4
<b><u>Total Correct</u></b>	<b><u>94.8</u></b>	<b><u>91.3</u></b>	<b><u>93.5</u></b>	<b><u>97.3</u></b>	<b><u>93.6</u></b>	<b><u>95.0</u></b>
Preferred	56.2	50.0	55.8	59.7	51.1	57.0
Acceptable	38.6	41.3	37.7	37.6	42.6	38.0
Total incorrect	5.2	8.8	6.5	2.7	6.4	5.1
<b><u>Confidence Intervals</u></b>						
Lower Bound	.9171	.8308	.8567	.9328	.8281	.9162
Upper Bound	.9678	.9573	.9719	.9894	.9780	.9706

ABCDE = Significantly higher than indicated cell at the 95% level of confidence.

**Q4.0** We would like to better understand what the package says to people. Please think of adult men and women who have a minor ache or pain—such as headache, toothache or backache --- or fever. Imagine that one of these people asked you about this product (*point to product*). For each of these people I describe, please tell me whether, according to the package label, it's OK for this person to take this product, it's not okay for them to take this product or (*pause*) they need to ask a doctor first before taking this product.

The choices are listed on this card. (*Hand Card 4.0*)

Let's start with (*Read X'd Type Of Person*). According to the package, is it OK for this person to take this product, it's not okay for them to take this product, or they need to ask a doctor first?

Table 17

SCENARIO LIST I (AIDED): THE PERSON WANTS TO GIVE THE PRODUCT IN THIS BOX TO HIS NINE YEAR OLD DAUGHTER WHO HAS A HEADACHE

	<u>Total</u>	<u>Age</u>			<u>Realm Score</u>	
		<u>18-34</u>	<u>35-49</u>	<u>50+</u>	<u>00-60</u>	<u>61-66</u>
Base: Total Respondents	(306)	(80)	(77)	(149)	(47)	(258)
	%	%	%	%	%	%
		(A)	(B)	(C)	(D)	(E)
Yes, okay (incorrect)	10.8	12.5	11.7	9.4	14.9	10.1
No, not okay (acceptable)	52.9	43.8	55.8	56.4	53.2	53.1
Needs to ask a doctor first (preferred)	35.0	43.8	32.5	31.5	31.9	35.3
Don't know (incorrect)	1.3	-	-	2.7	-	1.6
<b><u>Total Correct</u></b>	<b><u>87.9</u></b>	<b><u>87.5</u></b>	<b><u>88.3</u></b>	<b><u>87.9</u></b>	<b><u>85.1</u></b>	<b><u>88.4</u></b>
Preferred	35.0	43.8	32.5	31.5	31.9	35.3
Acceptable	52.9	43.8	55.8	56.4	53.2	53.1
Total incorrect	12.1	12.5	11.7	12.1	14.9	11.7
<b><u>Confidence Intervals</u></b>						
Lower Bound	.8377	.7850	.7924	.8169	.7231	.8392
Upper Bound	.9109	.9307	.9372	.9220	.9259	.9176

ABCDE = Significantly higher than indicated cell at the 95% level of confidence.

**Q4.0** We would like to better understand what the package says to people. Please think of adult men and women who have a minor ache or pain---such as headache, toothache or backache --- or fever. Imagine that one of these people asked you about this product (*point to product*). For each of these people I describe, please tell me whether, according to the package label, it's OK for this person to take this product, it's not okay for them to take this product or (*pause*) they need to ask a doctor first before taking this product.

The choices are listed on this card. (*Hand Card 4.0*)

Let's start with (*Read X'd Type Of Person*). According to the package, is it OK for this person to take this product, it's not okay for them to take this product, or they need to ask a doctor first?

Table 18

**SELECTED SCENARIOS (LIST I) AMONG THOSE NEEDING TO  
CONSULT A PHYSICIAN BEFORE USING ADVIL ANALGESIC**

- Percent Answering Correctly -

	Correct Responses	
	Need To Consult (138) %	Need To Consult And Said OK To Use Without Consulting With A Physician (99) %
Base: Total Respondents		
The person consumes three or more alcoholic drinks per day	92.0	92.9
<b><u>Confidence Levels</u></b>		
Lower Bound	.8626	.8608
Upper Bound	.9547	.9651
The person is under a doctor's care for an ulcer	88.4	88.9
<b><u>Confidence Levels</u></b>		
Lower Bound	.8199	.8120
Upper Bound	.9273	.9369
The person is currently taking a prescription medication for high blood pressure	84.8	84.8
<b><u>Confidence Levels</u></b>		
Lower Bound	.7787	.7644
Upper Bound	.8984	.9056
The last time the person took a pain reliever they developed stomach pain	92.8	93.9
<b><u>Confidence Levels</u></b>		
Lower Bound	.8723	.8735
Upper Bound	.9605	.9717

**Q4.0** We would like to better understand what the package says to people. Please think of adult men and women who have a minor ache or pain—such as headache, toothache or backache --- or fever. Imagine that one of these people asked you about this product (*point to product*). For each of these people I describe, please tell me whether, according to the package label, it's OK for this person to take this product, it's not okay for them to take this product or (*pause*) they need to ask a doctor first before taking this product.

The choices are listed on this card. (*Hand Card 4.0*)

Let's start with (*Read X'd Type Of Person*). According to the package, is it OK for this person to take this product, it's not okay for them to take this product, or they need to ask a doctor first?

Table 19

SELECTED SCENARIOS (LIST I) AMONG THOSE STATING THEY HAVE HAD  
AN ALLERGIC REACTION TO ANY OTHER PAIN RELIEVER/FEVER REDUCER

	Correct Responses	
	Allergic To Pain Relievers (26) <sup>c</sup> %	Allergic To Pain Relievers/Fever Reducers And OK To Use Without Consulting With A Physician (19) <sup>c</sup> %
Base: Total Respondents		
The person previously had an allergic reaction to a pain reliever	96.2	100.0
<b><u>Confidence Levels</u></b>		
Lower Bound	.8117	.8318
Upper Bound	.9933	1.00
The person is allergic to ibuprofen	88.5	89.5
<b><u>Confidence Levels</u></b>		
Lower Bound	.7107	.6864
Upper Bound	.9602	.9708
The last time the person took a pain reliever they developed stomach pain	100.0	100.0
<b><u>Confidence Levels</u></b>		
Lower Bound	.8713	.8318
Upper Bound	1.00	1.00

<sup>c</sup> Caution: Small base

**Q4.0** We would like to better understand what the package says to people. Please think of adult men and women who have a minor ache or pain—such as headache, toothache or backache — or fever. Imagine that one of these people asked you about this product (*point to product*). For each of these people I describe, please tell me whether, according to the package label, it's OK for this person to take this product, it's not okay for them to take this product or (*pause*) they need to ask a doctor first before taking this product.

The choices are listed on this card. (*Hand Card 4.0*)

Let's start with (*Read X'd Type Of Person*). According to the package, is it OK for this person to take this product, it's not okay for them to take this product, or they need to ask a doctor first?

Table 20

**WHETHER IT'S OKAY FOR A WOMAN WHO IS PREGNANT OR BREAST FEEDING  
TO TAKE ADVIL WITHOUT FIRST CONSULTING  
A HEALTHCARE PROFESSIONAL ACCORDING TO PACKAGE**

	<u>Total</u>	<u>Age</u>			<u>Realm Score</u>		<u>Gender</u>	
		<u>18-34</u>	<u>35-49</u>	<u>50+</u>	<u>00-60</u>	<u>61-66</u>	<u>Men</u>	<u>Women</u>
Base: Total Respondents	(306)	(80)	(77)	(149)	(47)	(258)	(153)	(153)
	%	%	%	%	%	%	%	%
		(A)	(B)	(C)	(D)	(E)	(F)	(G)
Okay (incorrect)	7.2	8.8	5.2	7.4	8.5	7.0	8.5	5.9
<b>Not okay / need to consult with a healthcare professional (correct)</b>	<b>90.5</b>	<b>88.8</b>	<b>93.5</b>	<b>89.9</b>	<b>87.2</b>	<b>91.1</b>	<b>88.2</b>	<b>92.8</b>
Don't know (incorrect)	2.3	2.5	1.3	2.7	4.3	1.9	3.3	1.3
<b><u>Confidence Intervals</u></b>								
Lower Bound	.8669	.8004	.8567	.8402	.7479	.8700	.8213	.8757
Upper Bound	.9330	.9400	.9719	.9378	.9399	.9400	.9240	.9593

ABCDEF = Significantly higher than indicated cell at the 95% level of confidence.

**Q5.5** According to what this package says, if a woman is pregnant or breast feeding, is it okay or not okay for her to take this product without first consulting with a healthcare professional?

Table 21

**WHETHER IT'S OKAY FOR A WOMAN TO TAKE ADVIL  
FOR MENSTRUAL CRAMPS DUE TO HER PERIOD ACCORDING TO PACKAGE**

	<u>Total</u>	<u>Age</u>			<u>Realm Score</u>		<u>Gender</u>	
		<u>18-34</u>	<u>35-49</u>	<u>50+</u>	<u>00-60</u>	<u>61-66</u>	<u>Men</u>	<u>Women</u>
Base: Total Respondents	(306)	(80)	(77)	(149)	(47)	(258)	(153)	(153)
	%	%	%	%	%	%	%	%
		(A)	(B)	(C)	(D)	(E)	(F)	(G)
Okay (preferred)	84.3	80.0	84.4	86.6	80.9	84.9	77.1	91.5F
Not okay (incorrect)	5.9	7.5	9.1	3.4	8.5	5.4	7.8	3.9
Should ask doctor first (acceptable)	8.5	11.3	6.5	8.1	6.4	8.9	12.4G	4.6
Don't know (incorrect)	1.3	1.3	-	2.0	4.3	0.8	2.6	-
<b><u>Total Correct</u></b>	<b><u>92.8</u></b>	<b><u>91.3</u></b>	<b><u>90.9</u></b>	<b><u>94.6</u></b>	<b><u>87.2</u></b>	<b><u>93.8</u></b>	<b><u>89.5</u></b>	<b><u>96.1F</u></b>
Preferred	84.3	80.0	84.4	86.6	80.9	84.9	77.1	91.5F
Acceptable	8.5	11.3	6.5	8.1	6.4	8.9	12.4G	4.6
Total incorrect	7.2	8.8	9.1	5.4	12.8	6.2	10.5G	3.9
<b><u>Confidence Intervals</u></b>								
Lower Bound	.8934	.8308	.8239	.8972	.7479	.9017	.8364	.9174
Upper Bound	.9520	.9573	.9552	.9723	.9399	.9615	.9343	.9820

ABCDEF G = Significantly higher than indicated cell at the 95% level of confidence.

**Q5.4** Suppose that a woman wanted to take this product for menstrual cramps due to her period. Is it OK for her to take this product, it's not okay for her to take this product or (*pause*) does she need to ask a doctor first before taking this product (*point to package*) for her menstrual cramps?

## **DOSING/DIRECTIONS FOR USE**

Table 22

**NUMBER OF TABLETS OF ADVIL  
A PERSON SHOULD INITIALLY TAKE ACCORDING TO PACKAGE**

	<u>Total</u> (306) %	<u>Age</u>			<u>Realm Score</u>	
		<u>18-34</u> (80) % (A)	<u>35-49</u> (77) % (B)	<u>50+</u> (149) % (C)	<u>00-60</u> (47) % (D)	<u>61-66</u> (258) % (E)
Base: Total Respondents						
<b><u>Correct (Net)</u></b>	<b><u>98.0</u></b>	<b><u>97.5</u></b>	<b><u>97.4</u></b>	<b><u>98.7</u></b>	<b><u>100.0</u></b>	<b><u>97.7</u></b>
One	68.3	63.8	63.6	73.2	61.7	69.4
Two	23.2	27.5	26.0	19.5	25.5	22.9
One or two	6.5	6.3	7.8	6.0	12.8	5.4
<b><u>Incorrect (Net)</u></b>	<b><u>1.3</u></b>	<b><u>2.5</u></b>	<b><u>1.3</u></b>	<b><u>0.7</u></b>	<b><u>-</u></b>	<b><u>1.6</u></b>
More than two at a time	0.3	1.3	-	-	-	0.4
Two or three	0.3	1.3	-	-	-	0.4
Six a day	0.3	-	-	0.7	-	0.4
Not more than 6	0.3	-	1.3	-	-	0.4
Don't know	0.7	-	1.3	0.7	-	0.8
<b><u>Confidence Intervals</u></b>						
Lower Bound	.9574	.9134	.9101	.9530	.9244	.9505
Upper Bound	.9907	.9931	.9928	.9965	1.00	.9895

ABCDE = Significantly higher than indicated cell at the 95% level of confidence.

Q7.0 Now, let's talk about directions for use. According to the package, how many tablets of this product should a person initially take?

Table 23

**MAXIMUM NUMBER OF TABLETS OF ADVIL A PERSON CAN TAKE  
WITHIN A FOUR TO SIX HOUR PERIOD ACCORDING TO PACKAGE**

	Total (306) %	Age			Realm Score	
		18-34 (80) % (A)	35-49 (77) % (B)	50+ (149) % (C)	00-60 (47) % (D)	61-66 (258) % (E)
Base: Total Respondents						
One (acceptable)	37.6	37.5	35.1	38.9	27.7	39.1
Two (preferred)	50.7	51.3	55.8	47.7	55.3	50.0
<u>Incorrect</u>	<u>8.8</u>	<u>7.5</u>	<u>6.5</u>	<u>10.7</u>	<u>10.6</u>	<u>8.5</u>
Three	0.3	-	-	0.7	-	0.4
Four	2.6	1.3	2.6	3.4	4.3	2.3
Three or four	0.3	1.3	-	-	-	0.4
Six	4.9	5.0	3.9	5.4	6.4	4.7
Eight	0.3	-	-	0.7	-	0.4
Ten	0.3	-	-	0.7	-	0.4
No more than six in 24 hours unless directed by doctor (undetermined)	0.7	1.3	-	0.7	2.1	0.4
Don't know (incorrect)	2.3	2.5	2.6	2.0	4.3	1.9
<b><u>Total Correct</u></b>	<b><u>88.2</u></b>	<b><u>88.8</u></b>	<b><u>90.9</u></b>	<b><u>86.6</u></b>	<b><u>83.0</u></b>	<b><u>89.1</u></b>
Preferred	50.7	51.3	55.8	47.7	55.3	50.0
Acceptable	37.6	37.5	35.1	38.9	27.7	39.1
Undetermined	0.7	1.3	-	0.7	2.1	0.4
Total incorrect	11.1	10.0	9.1	12.7	14.9	10.4
<b><u>Confidence Intervals</u></b>						
Lower Bound	.8410	.8004	.8239	.8020	.6988	.8471
Upper Bound	.9135	.9400	.9552	.9116	.9113	.9234

ABCDE = Significantly higher than indicated cell at the 95% level of confidence.

Q7.1 According to the package, what is the maximum tablets of this product a person can take within a four to six hour period?

Table 24

**MAXIMUM NUMBER OF TABLETS OF ADVIL A PERSON CAN TAKE  
WITHIN A 24 HOUR PERIOD ACCORDING TO PACKAGE**

	<u>Total</u> (306) %	<u>Age</u>			<u>Realm Score</u>	
		<u>18-34</u> (80) % (A)	<u>35-49</u> (77) % (B)	<u>50+</u> (149) % (C)	<u>00-60</u> (47) % (D)	<u>61-66</u> (258) % (E)
Base: Total Respondents						
Six (preferred)	91.8	91.3	84.4	96.0B	87.2	92.6
<u>Under-dosing (acceptable)</u>	<u>4.6</u>	<u>3.8</u>	<u>11.7C</u>	<u>1.3</u>	<u>12.8E</u>	<u>3.1</u>
Two	0.7	-	2.6C	-	4.3E	-
Four	3.3	3.8	6.5C	1.3	8.5E	2.3
Five	0.7	-	2.6C	-	-	0.8
<u>Over-dosing (incorrect)</u>	<u>2.9</u>	<u>3.8</u>	<u>2.6</u>	<u>2.7</u>	-	<u>3.5</u>
Seven	0.3	-	1.3	-	-	0.4
Eight	2.0	2.5	-	2.7	-	2.3
Ten	0.3	-	1.3	-	-	0.4
Eight to ten	0.3	1.3	-	-	-	0.4
Don't know (incorrect)	0.7	1.3	1.3	-	-	0.8
<b><u>Total Correct</u></b>	<b><u>96.4</u></b>	<b><u>95.0</u></b>	<b><u>96.1</u></b>	<b><u>97.3</u></b>	<b><u>100.0</u></b>	<b><u>95.7</u></b>
Preferred	91.8	91.3	84.4	96.0	87.2	92.6
Acceptable	4.6	3.8	11.7	1.3	12.8	3.1
Total incorrect	3.6	5.1	3.9	2.7	-	4.3
<b><u>Confidence Intervals</u></b>						
Lower Bound	.9367	.8784	.8915	.9328	.9244	.9248
Upper Bound	.9798	.9804	.9866	.9894	1.00	.9758

ABCDE = Significantly higher than indicated cell at the 95% level of confidence.

Q7.3 According to the package, what is the maximum number of tablets of this product a person should take within a 24 hour period?

Table 25

WHETHER IT'S OKAY TO TAKE ADVIL ALONG WITH ANOTHER PRODUCT  
CONTAINING IBUPROFEN ACCORDING TO PACKAGE

	<u>Total</u>	<u>Age</u>			<u>Realm Score</u>	
		<u>18-34</u>	<u>35-49</u>	<u>50+</u>	<u>00-60</u>	<u>61-66</u>
Base: Total Respondents	(306)	(80)	(77)	(149)	(47)	(258)
	%	%	%	%	%	%
		(A)	(B)	(C)	(D)	(E)
Okay (incorrect)	13.4	11.3	19.5	11.4	17.0	12.8
Not okay (acceptable)	33.3	36.3	37.7	29.5	34.0	32.9
Should ask doctor first (preferred)	52.3	51.3	41.6	58.4B	48.9	53.1
Don't know (incorrect)	1.0	1.3	1.3	0.7	-	1.2
<b><u>Total Correct</u></b>	<b><u>85.6</u></b>	<b><u>87.5</u></b>	<b><u>79.2</u></b>	<b><u>87.9</u></b>	<b><u>83.0</u></b>	<b><u>86.0</u></b>
Preferred	52.3	51.3	41.6	58.4	48.9	53.1
Acceptable	33.3	36.3	37.7	29.5	34.0	32.9
Total incorrect	14.4	12.6	20.8	12.1	17.0	14.0
<b><u>Confidence Intervals</u></b>						
Lower Bound	.8122	.7850	.6886	.8169	.6988	.8124
Upper Bound	.8909	.9307	.8677	.9220	.9113	.8971

ABCDE = Significantly higher than indicated cell at the 95% level of confidence.

Q5.0 According to what this package says, is it okay or not okay for a person to take this product (*point to package*) along with another product containing ibuprofen?

Table 26

WHETHER IT'S OKAY TO TAKE ADVIL ALONG WITH A TABLET OF ANOTHER PAIN RELIEVER SUCH AS TYLENOL ACCORDING TO PACKAGE

	<u>Total</u>	<u>Age</u>			<u>Realm Score</u>	
		<u>18-34</u>	<u>35-49</u>	<u>50+</u>	<u>00-60</u>	<u>61-66</u>
Base: Total Respondents	(306)	(80)	(77)	(149)	(47)	(258)
	%	%	%	%	%	%
		(A)	(B)	(C)	(D)	(E)
Okay (incorrect)	19.0	17.5	20.8	18.8	25.5	17.8
Not okay (acceptable)	38.2	45.0	37.7	34.9	44.7	37.2
Should ask doctor first (preferred)	40.5	35.0	40.3	43.6	27.7	42.6
Don't know (incorrect)	2.3	2.5	1.3	2.7	2.1	2.3
<b><u>Total Correct</u></b>	<b><u>78.8</u></b>	<b><u>80.0</u></b>	<b><u>77.9</u></b>	<b><u>78.5</u></b>	<b><u>72.3</u></b>	<b><u>79.8</u></b>
Preferred	40.5	35.0	40.3	43.6	27.7	42.6
Acceptable	38.2	45.0	37.7	34.9	44.7	37.2
Total incorrect	21.3	20.0	22.1	21.5	27.6	20.1
<b><u>Confidence Intervals</u></b>						
Lower Bound	.7388	.6995	.6743	.7123	.5820	.7448
Upper Bound	.8301	.8730	.8572	.8434	.8303	.8425

ABCDE = Significantly higher than indicated cell at the 95% level of confidence.

Q5.1 According to what this package says, is it okay or not okay for a person to take this product (*point to package*) along with a tablet of a pain reliever such as Tylenol?

Table 27

**WHETHER IT'S OKAY TO TAKE ADVIL WHEN ALSO TAKING  
A MULTI-SYMP TOM\_COLD OR FLU MEDICATION  
CONTAINING A PAIN RELIEVER ACCORDING TO PACKAGE**

	Total	Age			Realm Score	
		18-34	35-49	50+	00-60	61-66
Base: Total Respondents	(306)	(80)	(77)	(149)	(47)	(258)
	%	%	%	%	%	%
		(A)	(B)	(C)	(D)	(E)
Okay (incorrect)	20.9	16.3	28.6	19.5	27.7	19.8
Not okay (acceptable)	31.4	35.0	33.8	28.2	36.2	30.6
Should ask doctor first (preferred)	46.4	48.8	36.4	50.3B	36.2	48.1
Don't know (incorrect)	1.3	-	1.3	2.0	-	1.6
<b><u>Total Correct</u></b>	<b><u>77.8</u></b>	<b><u>83.8</u></b>	<b><u>70.1</u></b>	<b><u>78.5</u></b>	<b><u>72.3</u></b>	<b><u>78.7</u></b>
Preferred	46.4	48.8	36.4	50.3	36.2	48.1
Acceptable	31.4	35.0	33.8	28.2	36.2	30.6
Total incorrect	22.2	16.3	29.9	21.5	27.7	21.4
<b><u>Confidence Intervals</u></b>						
Lower Bound	.7281	.7421	.5912	.7123	.5820	.7330
Upper Bound	.8210	.9029	.7917	.8434	.8303	.8326

ABCDE = Significantly higher than indicated cell at the 95% level of confidence.

**Q5.3** According to what this package says, is it okay or not okay for a person to take this product (*point to package*) if they are also taking a Multi-Symptom cold or flu medication containing a pain reliever?

Table 28

WHETHER IT'S OKAY TO TAKE ADVIL WHEN ALSO TAKING  
A VITAMIN PILL ON A DAILY BASIS ACCORDING TO PACKAGE

	<u>Total</u>	<u>Age</u>			<u>Realm Score</u>	
		<u>18-34</u>	<u>35-49</u>	<u>50+</u>	<u>00-60</u>	<u>61-66</u>
Base: Total Respondents	(306)	(80)	(77)	(149)	(47)	(258)
	%	%	%	%	%	%
		(A)	(B)	(C)	(D)	(E)
Okay (preferred)	81.0	68.8	80.5	87.9A	83.0	80.6
Not okay (incorrect)	2.6	3.8	3.9	1.3	8.5E	1.6
Should ask doctor first (acceptable)	15.4	27.5BC	14.3	9.4	8.5	16.7
Don't know (incorrect)	1.0	-	1.3	1.3	-	1.2
<b><u>Total Correct</u></b>	<b><u>96.4</u></b>	<b><u>96.3</u></b>	<b><u>94.8</u></b>	<b><u>97.3</u></b>	<b><u>91.5</u></b>	<b><u>97.3</u></b>
Preferred	81.0	68.8	80.5	87.9	83.0	80.6
Acceptable	15.4	27.5	14.3	9.4	8.5	16.7
Total incorrect	3.6	3.8	5.2	2.6	8.5	2.8
<b><u>Confidence Intervals</u></b>						
Lower Bound	.9367	.8961	.8738	.9328	.8008	.9452
Upper Bound	.9798	.9874	.9796	.9894	.9665	.9869

ABCDE = Significantly higher than indicated cell at the 95% level of confidence.

**Q5.2** According to what this package says, is it okay or not okay for a person to take this product (*point to package*) if they are also taking a vitamin pill on a daily basis?

# **WHEN TO DISCONTINUE USE OF ADVIL**

Table 29

**SCENARIO LIST II (AIDED):  
THE PERSON DEVELOPS AN ALLERGIC REACTION TO THIS PRODUCT**

	<u>Total</u>	<u>Age</u>			<u>Realm Score</u>	
		<u>18-34</u>	<u>35-49</u>	<u>50+</u>	<u>00-60</u>	<u>61-66</u>
Base: Total Respondents	(306)	(80)	(77)	(149)	(47)	(258)
	%	%	%	%	%	%
		(A)	(B)	(C)	(D)	(E)
Continue to take the product when needed (incorrect)	2.9	1.3	6.5	2.0	4.3	2.7
Stop taking product and see doctor (correct)	97.1	98.8	93.5	98.0	95.7	97.3
<b><u>Confidence Intervals</u></b>						
Lower Bound	.9456	.9333	.8567	.9427	.8569	.9452
Upper Bound	.9847	.9979	.9719	.9932	.9881	.9869

**Q6.0** Now, I'm going to describe to you different things that a person may or may not experience while taking this product. For each, I'd like to know what the package tells you a person should do if they were taking this product and this happened. Specifically, should the person continue to take this product when needed or *(Pause)* should the person stop taking this product and see a doctor. To help you answer this question, this card lists the possible answers **(Hand Card 6.0)**. Let's start with *(Read X'd scenario)*. According to the package, should the person continue to take this product when needed or *(Pause)* should the person stop taking this product and see a doctor?

Table 30

SCENARIO LIST II (AIDED):  
AFTER TAKING THE ONE DOSE OF THIS PRODUCT,  
THE PERSON'S MUSCLE ACHE GOT SOMEWHAT BETTER

	<u>Total</u>	<u>Age</u>			<u>Realm Score</u>	
		<u>18-34</u>	<u>35-49</u>	<u>50+</u>	<u>00-60</u>	<u>61-66</u>
Base: Total Respondents	(306)	(80)	(77)	(149)	(47)	(258)
	%	%	%	%	%	%
		(A)	(B)	(C)	(D)	(E)
<b>Continue to take the product when needed (correct)</b>	<b>92.2</b>	<b>93.8</b>	<b>93.5</b>	<b>90.6</b>	<b>89.4</b>	<b>92.6</b>
Stop taking product and see doctor (incorrect)	7.5	6.3	6.5	8.7	10.6	7.0
Don't know (incorrect)	0.3	-	-	0.7	-	0.4
<b><u>Confidence Intervals</u></b>						
Lower Bound	.8865	.8625	.8567	.8484	.7745	.8874
Upper Bound	.9471	.9733	.9719	.9432	.9539	.9521

**Q6.0** Now, I'm going to describe to you different things that a person may or may not experience while taking this product. For each, I'd like to know what the package tells you a person should do if they were taking this product and this happened. Specifically, should the person continue to take this product when needed or (*Pause*) should the person stop taking this product and see a doctor. To help you answer this question, this card lists the possible answers (*Hand Card 6.0*). Let's start with (*Read X'd scenario*). According to the package, should the person continue to take this product when needed or (*Pause*) should the person stop taking this product and see a doctor?

Table 31

**SCENARIO LIST II (AIDED): THE PERSON FEELS  
HE / SHE NEEDS TO TAKE THIS PRODUCT FOR MORE THAN TEN DAYS**

	Total	Age			Realm Score	
		18-34	35-49	50+	00-60	61-66
Base: Total Respondents	(306)	(80)	(77)	(149)	(47)	(258)
	%	%	%	%	%	%
		(A)	(B)	(C)	(D)	(E)
Continue to take the product when needed (incorrect)	15.0	10.0	13.0	18.8	21.3	14.0
Stop taking product and see doctor (correct)	83.0	90.0C	84.4	78.5	78.7	83.7
Don't know (incorrect)	2.0	-	2.6	2.7	-	2.3
<b><u>Confidence Intervals</u></b>						
Lower Bound	.7839	.8149	.7469	.7123	.6507	.7870
Upper Bound	.8679	.9485	.9084	.8434	.8799	.8771

ABCDE = Significantly higher than indicated cell at the 95% level of confidence.

**Q6.0** Now, I'm going to describe to you different things that a person may or may not experience while taking this product. For each, I'd like to know what the package tells you a person should do if they were taking this product and this happened. Specifically, should the person continue to take this product when needed or (*Pause*) should the person stop taking this product and see a doctor. To help you answer this question, this card lists the possible answers (**Hand Card 6.0**). Let's start with (*Read X'd scenario*). According to the package, should the person continue to take this product when needed or (*Pause*) should the person stop taking this product and see a doctor?

Table 32

**SCENARIO LIST II (AIDED):  
THE PERSON DEVELOPS STOMACH PAIN AFTER USING THIS PRODUCT**

	<u>Total</u>	<u>Age</u>			<u>Realm Score</u>	
		<u>18-34</u>	<u>35-49</u>	<u>50+</u>	<u>00-60</u>	<u>61-66</u>
Base: Total Respondents	(306)	(80)	(77)	(149)	(47)	(258)
	%	%	%	%	%	%
		(A)	(B)	(C)	(D)	(E)
Continue to take the product when needed (incorrect)	2.0	1.3	6.5C	-	6.4E	1.2
Stop taking product and see doctor (correct)	97.7	98.8	93.5	99.3B	93.6	98.4D
Don't know (incorrect)	0.3	-	-	0.7	-	0.4
<b><u>Confidence Intervals</u></b>						
Lower Bound	.9534	.9333	.8567	.9625	.8281	.9601
Upper Bound	.9888	.9979	.9719	.9987	.9780	.9937

ABCDE = Significantly higher than indicated cell at the 95% level of confidence.

**Q6.0** Now, I'm going to describe to you different things that a person may or may not experience while taking this product. For each, I'd like to know what the package tells you a person should do if they were taking this product and this happened. Specifically, should the person continue to take this product when needed or (*Pause*) should the person stop taking this product and see a doctor. To help you answer this question, this card lists the possible answers (**Hand Card 6.0**). Let's start with (*Read X'd scenario*). According to the package, should the person continue to take this product when needed or (*Pause*) should the person stop taking this product and see a doctor?

Table 33

**SCENARIO LIST II (AIDED): THE PERSON TOOK THIS PRODUCT FOR A LEG INJURY WHICH NOW HAS BECOME RED AND SWOLLEN**

	Total	Age			Realm Score	
		18-34	35-49	50+	00-60	61-66
Base: Total Respondents	(306)	(80)	(77)	(149)	(47)	(258)
	%	%	%	%	%	%
		(A)	(B)	(C)	(D)	(E)
Continue to take the product when needed (incorrect)	5.2	3.8	13.0AC	2.0	4.3	5.0
Stop taking product and see doctor (correct)	94.1	95.0	85.7	98.0B	95.7	94.2
Don't know (incorrect)	0.7	1.3	1.3	-	-	0.8
<b><u>Confidence Intervals</u></b>						
Lower Bound	.9087	.8784	.7619	.9427	.8569	.9065
Upper Bound	.9623	.9804	.9182	.9932	.9881	.9646

ABCDE = Significantly higher than indicated cell at the 95% level of confidence.

**Q6.0** Now, I'm going to describe to you different things that a person may or may not experience while taking this product. For each, I'd like to know what the package tells you a person should do if they were taking this product and this happened. Specifically, should the person continue to take this product when needed or (*Pause*) should the person stop taking this product and see a doctor. To help you answer this question, this card lists the possible answers (*Hand Card 6.0*). Let's start with (*Read X'd scenario*). According to the package, should the person continue to take this product when needed or (*Pause*) should the person stop taking this product and see a doctor?

Table 34

**SCENARIO LIST II (AIDED): THE PERSON STARTS USING A  
NON-PRESCRIPTION ANTIBIOTIC CREAM FOR A FEW DAYS FOR A MINOR WOUND**

	<u>Total</u>	<u>Age</u>			<u>Realm Score</u>	
		<u>18-34</u>	<u>35-49</u>	<u>50+</u>	<u>00-60</u>	<u>61-66</u>
Base: Total Respondents	(306)	(80)	(77)	(149)	(47)	(258)
	%	%	%	%	%	%
		(A)	(B)	(C)	(D)	(E)
<b>Continue to take the product when needed (correct)</b>	<b>70.6</b>	<b>78.8</b>	<b>68.8</b>	<b>67.1</b>	<b>48.9</b>	<b>74.4D</b>
Stop taking product and see doctor (incorrect)	25.5	18.8	27.3	28.2	48.9E	21.3
Don't know (incorrect)	3.9	2.5	3.9	4.7	2.1	4.3
<b><u>Confidence Intervals</u></b>						
Lower Bound	.6527	.6863	.5777	.5921	.3524	.6874
Upper Bound	.7542	.8633	.7805	.7413	.6272	.7934

ABCDE = Significantly higher than indicated cell at the 95% level of confidence.

**Q6.0** Now, I'm going to describe to you different things that a person may or may not experience while taking this product. For each, I'd like to know what the package tells you a person should do if they were taking this product and this happened. Specifically, should the person continue to take this product when needed or (*Pause*) should the person stop taking this product and see a doctor. To help you answer this question, this card lists the possible answers (*Hand Card 6.0*). Let's start with (*Read X'd scenario*). According to the package, should the person continue to take this product when needed or (*Pause*) should the person stop taking this product and see a doctor?

Table 35

**SCENARIO LIST II (AIDED): THE PERSON STARTED USING THIS PRODUCT  
LAST NIGHT AND THEIR TOOTHACHE PAIN SUBSIDED SOMEWHAT**

Base: Total Respondents	Total	Age			Realm Score	
		18-34	35-49	50+	00-60	61-66
	(306)	(80)	(77)	(149)	(47)	(258)
	%	%	%	%	%	%
		(A)	(B)	(C)	(D)	(E)
<b>Continue to take the product when needed (correct)</b>	<b>89.2</b>	<b>87.5</b>	<b>89.6</b>	<b>89.9</b>	<b>83.0</b>	<b>90.3</b>
Stop taking product and see doctor (incorrect)	10.5	11.3	10.4	10.1	17.0	9.3
Don't know (incorrect)	0.3	1.3	-	-	-	0.4
<b><u>Confidence Intervals</u></b>						
Lower Bound	.8522	.7850	.8080	.8402	.6988	.8608
Upper Bound	.9220	.9307	.9463	.9378	.9113	.9334

**Q6.0** Now, I'm going to describe to you different things that a person may or may not experience while taking this product. For each, I'd like to know what the package tells you a person should do if they were taking this product and this happened. Specifically, should the person continue to take this product when needed or (*Pause*) should the person stop taking this product and see a doctor. To help you answer this question, this card lists the possible answers (**Hand Card 6.0**). Let's start with (*Read X'd scenario*). According to the package, should the person continue to take this product when needed or (*Pause*) should the person stop taking this product and see a doctor?

Table 36

SCENARIO LIST II (AIDED): THE PERSON TOOK THIS PRODUCT  
LAST NIGHT FOR A FEVER WHICH TODAY HAS BECOME WORSE

	Total	Age			Realm Score	
		18-34	35-49	50+	00-60	61-66
Base: Total Respondents	(306)	(80)	(77)	(149)	(47)	(258)
	%	%	%	%	%	%
		(A)	(B)	(C)	(D)	(E)
Continue to take the product when needed (incorrect)	12.1	12.5	16.9	9.4	14.9	11.6
<b>Stop taking product and see doctor (correct)</b>	<b>86.9</b>	<b>87.5</b>	<b>83.1</b>	<b>88.6</b>	<b>85.1</b>	<b>87.2</b>
Don't know (incorrect)	1.0	-	-	2.0	-	1.2
<b><u>Confidence Intervals</u></b>						
Lower Bound	.8266	.7850	.7321	.8250	.7231	.8257
Upper Bound	.9023	.9307	.8985	.9276	.9259	.9074

**Q6.0** Now, I'm going to describe to you different things that a person may or may not experience while taking this product. For each, I'd like to know what the package tells you a person should do if they were taking this product and this happened. Specifically, should the person continue to take this product when needed or (*Pause*) should the person stop taking this product and see a doctor. To help you answer this question, this card lists the possible answers (**Hand Card 6.0**). Let's start with (*Read X'd scenario*). According to the package, should the person continue to take this product when needed or (*Pause*) should the person stop taking this product and see a doctor?

Table 37

**SCENARIO LIST II (AIDED): THE PERSON  
DEVELOPED NEW OR UNEXPECTED SYMPTOMS AFTER USING THIS PRODUCT**

	<u>Total</u>	<u>Age</u>			<u>Realm Score</u>	
		<u>18-34</u>	<u>35-49</u>	<u>50+</u>	<u>00-60</u>	<u>61-66</u>
Base: Total Respondents	(306)	(80)	(77)	(149)	(47)	(258)
	%	%	%	%	%	%
		(A)	(B)	(C)	(D)	(E)
Continue to take the product when needed (incorrect)	1.6	3.8C	2.6C	-	2.1	1.6
Stop taking product and see doctor (correct)	98.4	96.3	97.4	100.0AB	97.9	98.4
<b><u>Confidence Intervals</u></b>						
Lower Bound	.9628	.8961	.9101	.9749	.8893	.9601
Upper Bound	.9932	.9874	.9928	1.00	.9963	.9937

ABCDE = Significantly higher than indicated cell at the 95% level of confidence.

**Q6.0** Now, I'm going to describe to you different things that a person may or may not experience while taking this product. For each, I'd like to know what the package tells you a person should do if they were taking this product and this happened. Specifically, should the person continue to take this product when needed or *(Pause)* should the person stop taking this product and see a doctor. To help you answer this question, this card lists the possible answers (Hand Card 6.0). Let's start with *(Read X'd scenario)*. According to the package, should the person continue to take this product when needed or *(Pause)* should the person stop taking this product and see a doctor?

Table 38

**SCENARIO LIST II (AIDED): THE PERSON  
TOOK THIS PRODUCT FOR A FEVER FOR THREE DAYS AND STILL HAS A FEVER**

	<u>Total</u>	<u>Age</u>			<u>Realm Score</u>	
		<u>18-34</u>	<u>35-49</u>	<u>50+</u>	<u>00-60</u>	<u>61-66</u>
Base: Total Respondents	(306)	(80)	(77)	(149)	(47)	(258)
	%	%	%	%	%	%
		(A)	(B)	(C)	(D)	(E)
Continue to take the product when needed (incorrect)	4.9	8.8C	5.2	2.7	8.5	4.3
Stop taking product and see doctor (correct)	95.1	91.3	94.8	97.3A	91.5	95.7
<b><u>Confidence Intervals</u></b>						
Lower Bound	.9207	.8308	.8738	.9328	.8008	.9248
Upper Bound	.9701	.9573	.9796	.9894	.9665	.9758

ABCDE = Significantly higher than indicated cell at the 95% level of confidence.

**Q6.0** Now, I'm going to describe to you different things that a person may or may not experience while taking this product. For each, I'd like to know what the package tells you a person should do if they were taking this product and this happened. Specifically, should the person continue to take this product when needed or *(Pause)* should the person stop taking this product and see a doctor. To help you answer this question, this card lists the possible answers **(Hand Card 6.0)**. Let's start with *(Read X'd scenario)*. According to the package, should the person continue to take this product when needed or *(Pause)* should the person stop taking this product and see a doctor?

Table 39

**SCENARIO LIST II (AIDED): THE PERSON HAS ARTHRITIS PAIN  
WHICH THEY WANT TO TREAT FOR THREE OR FOUR DAYS**

	Total	Age			Realm Score	
		18-34	35-49	50+	00-60	61-66
Base: Total Respondents	(306)	(80)	(77)	(149)	(47)	(258)
	%	%	%	%	%	%
		(A)	(B)	(C)	(D)	(E)
<b>Continue to take the product when needed (correct)</b>	<b>78.4</b>	<b>78.8</b>	<b>80.5</b>	<b>77.2</b>	<b>78.7</b>	<b>78.3</b>
Stop taking product and see doctor (incorrect)	18.0	17.5	19.5	17.4	17.0	18.2
Don't know (incorrect)	3.6	3.8	-	5.4B	4.3	3.5
<b><u>Confidence Intervals</u></b>						
Lower Bound	.7345	.6863	.7029	.6983	.6507	.7287
Upper Bound	.8264	.8633	.8781	.8320	.8799	.8289

ABCDE = Significantly higher than indicated cell at the 95% level of confidence.

**Q6.0** Now, I'm going to describe to you different things that a person may or may not experience while taking this product. For each, I'd like to know what the package tells you a person should do if they were taking this product and this happened. Specifically, should the person continue to take this product when needed or (*Pause*) should the person stop taking this product and see a doctor. To help you answer this question, this card lists the possible answers (**Hand Card 6.0**). Let's start with (*Read X'd scenario*). According to the package, should the person continue to take this product when needed or (*Pause*) should the person stop taking this product and see a doctor?

**KNOWLEDGE OF SYMPTOMS OF  
ALLERGIC REACTION TO IBUPROFEN**

Table 40

**SYMPTOMS MIGHT EXPERIENCE  
IF HAVING AN ALLERGIC REACTION TO IBUPROFEN ACCORDING TO PACKAGE**

Base: Total Respondents	Total (306) %	Age			Realm Score	
		18-34 (80) % (A)	35-49 (77) % (B)	50+ (149) % (C)	00-60 (47) % (D)	61-66 (258) % (E)
<b><u>Listed Correct Symptoms (Net)</u></b>	<b><u>89.2</u></b>	<b><u>83.8</u></b>	<b><u>90.9</u></b>	<b><u>91.3</u></b>	<b><u>89.4</u></b>	<b><u>89.1</u></b>
Hives	82.0	76.3	83.1	84.6	74.5	83.3
Facial swelling	72.2	66.3	75.3	73.8	63.8	73.6
Asthma or wheezing	67.0	70.0	64.9	66.4	53.2	69.4D
Shock	62.4	57.5	63.6	64.4	51.1	64.3
<b><u>Symptoms Not Listed (Net)</u></b>	<b><u>11.4</u></b>	<b><u>11.3</u></b>	<b><u>11.7</u></b>	<b><u>11.4</u></b>	<b><u>8.5</u></b>	<b><u>12.0</u></b>
Stomach pain	5.2	2.5	7.8	5.4	6.4	5.0
Fever	2.6	2.5	1.3	3.4	2.1	2.7
Skin irritation	2.0	5.0C	1.3	0.7	-	2.3
Nausea	2.0	1.3	2.6	2.0	-	2.3
Headaches	2.0	1.3	1.3	2.7	2.1	1.9
Pain	1.3	5.0BC	-	-	-	1.6
Body swells	1.0	-	2.6	0.7	-	1.2
<b><u>Confidence Intervals</u></b>						
Lower Bound	.8522	.7421	.8239	.8567	.7745	.8471
Upper Bound	.9220	.9029	.9552	.9485	.9539	.9234

ABCDE = Significantly higher than indicated cell at the 95% level of confidence.

Q6.5 According to the package, what symptoms might you experience if you were having an allergic reaction to ibuprofen?

# **PACKAGE READABILITY**

Table 41

PACKAGE READABILITY

	Total	Age			Realm Score	
		18-34	35-49	50+	00-60	61-66
Base: Total Respondents	(306)	(80)	(77)	(149)	(47)	(258)
	%	%	%	%	%	%
		(A)	(B)	(C)	(D)	(E)
<u>Easy</u>	<u>75.5</u>	<u>86.3C</u>	<u>74.0</u>	<u>70.5</u>	<u>76.6</u>	<u>75.2</u>
The print was very easy to see	31.4	40.0C	36.4	24.2	38.3	30.2
The print was easy to see	44.1	46.3	37.7	46.3	38.3	45.0
I could see it but had to strain to see the print	19.6	12.5	18.2	24.2A	17.0	20.2
<u>Difficult</u>	<u>4.9</u>	<u>1.3</u>	<u>7.8A</u>	<u>5.4</u>	<u>6.4</u>	<u>4.7</u>
I could make out just a little bit of the print	3.3	-	5.2A	4.0	2.1	3.5
I could hardly make out anything at all	1.6	1.3	2.6	1.3	4.3	1.2

ABCDE = Significantly higher than indicated cell at the 95% level of confidence.

Q8.0 Which one of the phrases listed on this card best describes how you feel about the size of print on the back of the package?

**PHYSICIAN RECOMMENDATION  
OF ADVIL/IBUPROFEN**

Table 42

WHETHER DOCTOR EVER RECOMMENDED ADVIL

	<u>Total</u>	<u>Age</u>			<u>Realm Score</u>	
		<u>18-34</u>	<u>35-49</u>	<u>50+</u>	<u>00-60</u>	<u>61-66</u>
Base: Total Respondents	(306)	(80)	(77)	(149)	(47)	(258)
	%	%	%	%	%	%
		(A)	(B)	(C)	(D)	(E)
Yes	45.8	41.3	50.6	45.6	44.7	46.1
No	52.0	58.8	46.8	51.0	53.2	51.6
Don't know	2.3	-	2.6	3.4	2.1	2.3

ABCDE = Significantly higher than indicated cell at the 95% level of confidence.

Q14.0 Has your doctor ever recommended that you take Advil?

Table 43

WHETHER DOCTOR EVER RECOMMENDED ADVIL

	<u>Need To Consult</u> (138) %	<u>No Need To Consult</u> (142) %	<u>Allergic to Pain Relievers</u> (26) <sup>c</sup> %
Base: Total Respondents			
Yes	49.3	41.5	50.0
No	49.3	54.9	50.0
Don't know	1.4	3.5	-

<sup>c</sup> Caution: Small base

**Q14.0** Has your doctor ever recommended that you take Advil?

Table 44

NUMBER OF TABLETS OF ADVIL PER DOSE DOCTOR RECOMMENDED

Base: Doctor Recommended Advil	<u>Total</u> (140) %
One	21.4
Two	47.1
One or two	8.6
Three	7.1
Four	3.6
Six	1.4
Seven	0.7
What package says	0.7
Doctor did not say	7.1
Don't know	2.1

Q14.1 The last time you spoke with your doctor about Advil, how many tablets of Advil per dose did your doctor recommend you take?

Table 45

LENGTH OF TIME DOCTOR RECOMMENDED TO TAKE ADVIL

Base: Doctor Recommended Advil	<u>Total</u> (140) %
For as long as needed	34.3
For a few days	11.4
<u>Number of Days</u>	
1	1.4
2	10.7
3	7.1
4	5.7
5	0.7
6	0.7
7	7.9
10	4.3
14	2.1
28	0.7
30	0.7
31 or more	4.3
Did not specify	2.9
Don't know	4.3

Q14.2 The last time you spoke to your doctor about Advil, for how long a period of time did your doctor recommend you take Advil?

Table 46

**WHETHER EVER ASKED A DOCTOR  
IF IT WAS OKAY TO TAKE ADVIL OR ANOTHER NON-PRESCRIPTION  
PAIN RELIEVER OR FEVER REDUCER CONTAINING IBUPROFEN**

	<u>Total</u>	<u>Age</u>			<u>Realm Score</u>	
		<u>18-34</u>	<u>35-49</u>	<u>50+</u>	<u>00-60</u>	<u>61-66</u>
Base: Total Respondents	(306)	(80)	(77)	(149)	(47)	(258)
	%	%	%	%	%	%
		(A)	(B)	(C)	(D)	(E)
Yes	39.5	31.3	44.2	41.6	31.9	41.1
No	59.8	67.5	54.5	58.4	63.8	58.9
Don't know	0.7	1.3	1.3	-	4.3E	-

ABCDE = Significantly higher than indicated cell at the 95% level of confidence.

**Q14.3** You may or may not have already mentioned this... Have you ever asked your doctor whether or not it was OK for you to take Advil or another non-prescription pain reliever or fever reducer that contains ibuprofen?

Table 47

**WHETHER EVER ASKED A DOCTOR  
IF IT WAS OKAY TO TAKE ADVIL OR ANOTHER NON-PRESCRIPTION  
PAIN RELIEVER OR FEVER REDUCER CONTAINING IBUPROFEN**

Base: Total Respondents	<u>Need To Consult</u> (138) %	<u>No Need To Consult</u> (142) %	<u>Allergic to Pain Relievers</u> (26) <sup>c</sup> %
Yes	44.2	33.8	46.2
No	55.8	64.8	53.8
Don't know	-	1.4	-

<sup>c</sup> Caution: Small base

**Q14.3** You may or may not have already mentioned this... Have you ever asked your doctor whether or not it was OK for you to take Advil or another non-prescription pain reliever or fever reducer that contains ibuprofen?

Table 48

WHETHER DOCTOR SAID IT WAS OKAY TO TAKE ADVIL OR ANOTHER  
NON-PRESCRIPTION PAIN RELIEVER OR FEVER REDUCER CONTAINING IBUPROFEN

	<u>Total</u>	<u>Age</u>			<u>Realm Score</u>	
		<u>18-34</u>	<u>35-49</u>	<u>50+</u>	<u>00-60</u>	<u>61-66</u>
Base: Asked Doctor If It Was Okay To Take Advil Or Another Non-Prescription Pain Reliever Or Fever Reducer Containing Ibuprofen	(121) %	(25) <sup>c</sup> %	(34) %	(62) %	(15) <sup>c</sup> %	(106) %
		(A)	(B)	(C)	(D)	(E)
Yes, okay	93.4	96.0	97.1	90.3	73.3	96.2
No, not okay	5.0	4.0	2.9	6.5	20.0	2.8
Don't know	1.7	-	-	3.2	6.7	0.9

<sup>c</sup> Caution: Small base

ABCDE = Significantly higher than indicated cell at the 95% level of confidence.

Q14.4 The last time you asked your doctor about Advil or another non-prescription pain reliever or fever reducer that contains Ibuprofen, did the doctor say it was Ok for you to take that type of product or Not Okay for you to take that type of product?

Table 49

WHETHER DOCTOR SAID IT WAS OKAY TO TAKE ADVIL OR ANOTHER  
NON-PRESCRIPTION PAIN RELIEVER OR FEVER REDUCER CONTAINING IBUPROFEN

	<u>Need To Consult</u>	<u>No Need To Consult</u>	<u>Allergic to Pain Relievers</u>
Base: Asked Doctor If It Was Okay To Take Advil Or Another Non-Prescription Pain Reliever Or Fever Reducer Containing Ibuprofen	(61) %	(48) %	(12) <sup>c</sup> %
Yes, okay	91.8	95.8	91.7
No, not okay	6.6	2.1	8.3
Don't know	1.6	2.1	-

<sup>c</sup> Caution: Small base

**Q14.4** The last time you asked your doctor about Advil or another non-prescription pain reliever or fever reducer that contains Ibuprofen, did the doctor say it was Ok for you to take that type of product or Not Okay for you to take that type of product?

Table 50

DOCTOR RECOMMENDED / SAID OKAY TO TAKE ADVIL

	<u>Total</u>	<u>Age</u>			<u>Realm Score</u>	
		<u>18-34</u>	<u>35-49</u>	<u>50+</u>	<u>00-60</u>	<u>61-66</u>
Base: Total Respondents	(306)	(80)	(77)	(149)	(47)	(258)
	%	%	%	%	%	%
		(A)	(B)	(C)	(D)	(E)
<b><u>Doctor Recommended/ Said Okay To Take (Net)</u></b>	<b><u>59.5</u></b>	<b><u>52.5</u></b>	<b><u>66.2</u></b>	<b><u>59.7</u></b>	<b><u>53.2</u></b>	<b><u>60.9</u></b>
Doctor recommended only	22.5	22.5	23.4	22.1	29.8	21.3
Said okay to take only	13.7	11.3	15.6	14.1	8.5	14.7
Both	23.2	18.8	27.3	23.5	14.9	24.8

ABCDE = Significantly higher than indicated cell at the 95% level of confidence.

**Q14.0** Has your doctor ever recommended that you take Advil?

**Q14.4** The last time you asked your doctor about Advil or another non-prescription pain reliever or fever reducer that contains Ibuprofen, did the doctor say it was Ok for you to take that type of product or Not Okay for you to take that type of product?

Table 51

DOCTOR RECOMMENDED / SAID OKAY TO TAKE ADVIL

	<u>Need To Consult</u> (138) %	<u>No Need To Consult</u> (142) %	<u>Allergic to Pain Relievers</u> (26) <sup>c</sup> %
Base: Total Respondents			
<b><u>Doctor Recommended/ Said Okay To Take (Net)</u></b>	<b><u>64.5</u></b>	<b><u>52.8</u></b>	<b><u>69.2</u></b>
Doctor recommended only	23.9	20.4	26.9
Said okay to take only	15.2	11.3	19.2
Both	25.4	21.1	23.1

<sup>c</sup> Caution: Small base

Q14.0 Has your doctor ever recommended that you take Advil?

Q14.4 The last time you asked your doctor about Advil or another non-prescription pain reliever or fever reducer that contains Ibuprofen, did the doctor say it was Ok for you to take that type of product or Not Okay for you to take that type of product?

# **PROFILE OF RESPONDENTS**

Table 52

AGE AND GENDER OF RESPONDENTS

Base: Total Respondents	<u>Total</u> (306) %
<u>Age</u>	
18 - 34	26.1
35 - 49	25.2
50 +	48.7
Mean	46.2
<u>Gender</u>	
Male	50.0
Female	50.0

Scr Q5.0 Which of the following categories includes your age?

Scr Q5.5 Gender (*Record respondent gender*)

Table 53

WHETHER UNDER DOCTOR'S CARE FOR A CONTINUING MEDICAL CONDITION

Base: Total Respondents	<u>Total</u> (306) %
Yes	30.7
No	69.0
Don't know	0.3

Q9.0 Are you currently under a doctor's care for a continuing medical condition?

Table 54

CONTINUING MEDICAL CONDITION FOR WHICH UNDER A DOCTOR'S CARE

Base: Under Doctor's Care for Continuing Medical Condition	<u>Total</u> (94) %
Blood pressure/high blood pressure	31.9
Cholesterol/high cholesterol	17.0
Arthritis	13.8
Diabetes	10.6
Thyroid disease	10.6
Depression	7.4
Heart condition/heart disease	7.4
Cancer/chemotherapy	5.3
Asthma	4.3
Migraines	2.1
Pregnancy	2.1
Broken bone	2.1
Muscle pain	2.1
Hypertension	2.1

**Q9.5** For which specific continuing medical condition or conditions do you see or consult with a doctor?

Table 55

WHETHER CURRENTLY TAKING ANY PRESCRIPTION  
OR NON-PRESCRIPTION DRUGS ON A REGULAR BASIS

Base: Total Respondents	<u>Total</u> (306) %
Yes	40.8
No	58.8
Don't know	0.3

9.8 Excluding vitamins are you currently taking any prescription or non-prescription drugs on a regular basis?

Table 56

TYPE OF DRUGS TAKE ON A REGULAR BASIS

Base: Take Drugs on a Regular Basis	<u>Total</u> (125) %
Prescription medications	55.2
Non-prescription medications	11.2
Both prescription and non-prescription medications	33.6

Q9.9 Are the drugs you take on a regular basis. . .

Table 57

**WHETHER EVER HAD AN ALLERGIC REACTION  
TO ANY PAIN RELIEVER OR FEVER REDUCER**

	<u>Total</u> (306) %
Base: Total Respondents	
Yes	8.5
No	91.5

**Q10.0** Have you ever had an allergic reaction to any pain reliever or fever reducer?

Table 58

WHETHER EVER HAD ANY PROBLEMS  
OR SIDE EFFECTS WITH ANY PAIN RELIEVER OR FEVER REDUCER

Base: Total Respondents	<u>Total</u> (306) %
Yes	9.8
No	89.9
Don't know	0.3

Q11.0 You may or may not have already mentioned this ... Have you ever had problems or side effects with any pain reliever or fever reducer?

Table 59

WHETHER PREGNANT OR BREAST FEEDING  
- Among Females -

Base: Females	<u>Total</u> (153) %
Yes	2.0
No	95.4
Don't know	2.6

Q12.0 Are you pregnant or breast feeding?

Table 60

NUMBER OF ALCOHOLIC DRINKS CONSUME IN A TYPICAL DAY

Base: Total Respondents	<u>Total</u> (306) %
None	77.1
One	11.8
Two	5.9
Three or more	4.2
Don't know	1.0

Q13.0 Which letter on this card best describes how many alcoholic drinks you consume in a typical day?

Table 61

ETHNICITY

Base: Total Respondents	<u>Total</u> (306) %
White/Caucasian	72.9
African-American/Black	16.0
Hispanic/Latino	8.5
Asian	1.3
American Indian	0.3
Other	0.7
Refused	0.3

Q15.0 Which letter on this card best describes your ethnic or racial background?

Table 62

REALM SCORE

Base: Total Respondents	<u>Total</u> (306) %
0 - 60 (8 <sup>th</sup> grade or less)	15.4
61 - 66	84.3
No answer	0.3

Scr Q9.0 (When respondent is at facility, administer REALM test)

**APPENDICES**

x i

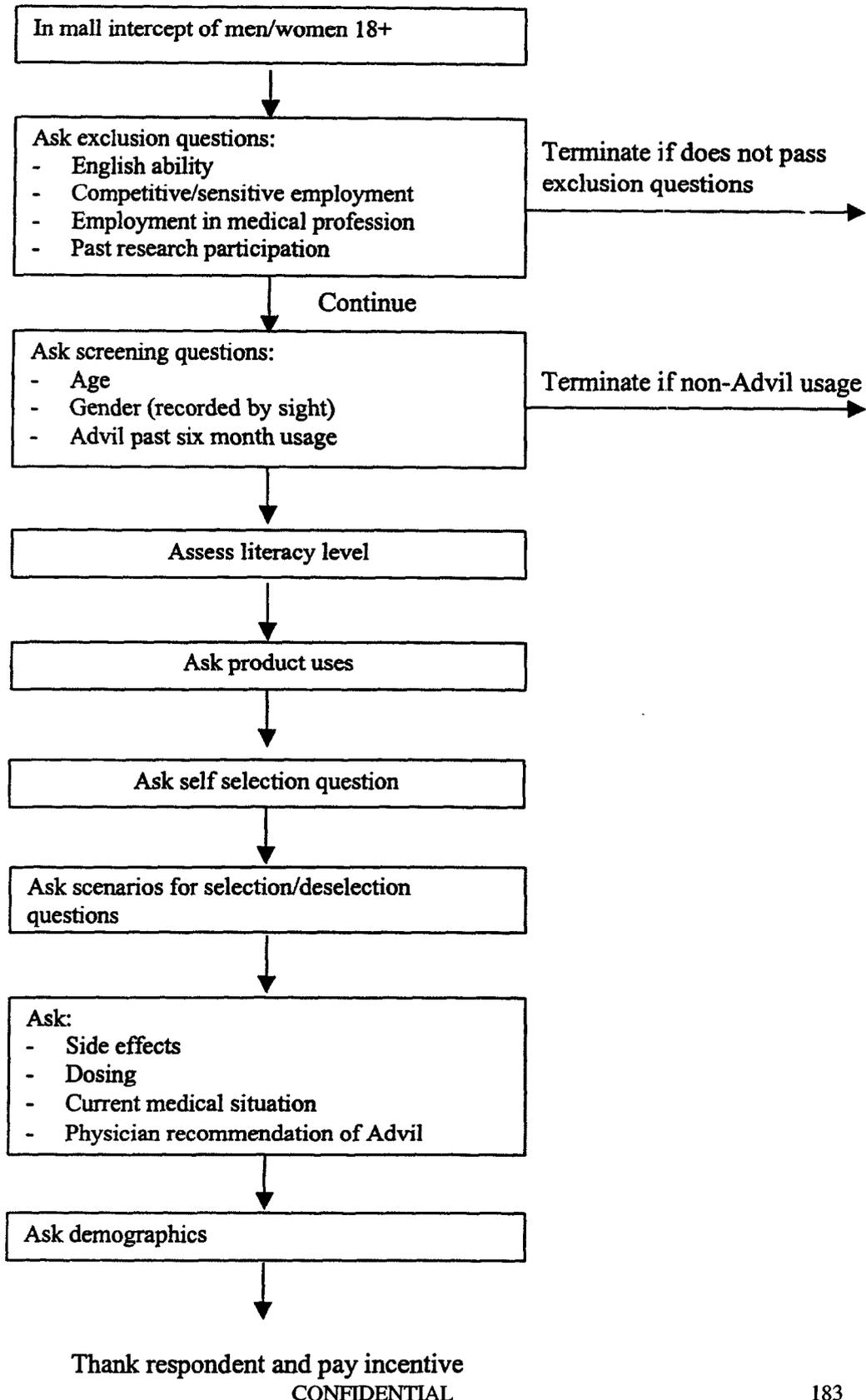
**APPENDIX A**  
**SAMPLE DISTRIBUTION**

## Sample Distribution

	<u>Total</u> N
Need To Consult	138
No Need to Consult	142
Allergic to Pain Relievers	26
<u>Age</u>	
18 - 34	80
35 - 49	77
50 +	149
<u>Gender</u>	
Men	153
Women	153
<u>REALM Score</u>	
0 - 60	47
61 - 66	258
Not Ascertained	1
<b>Total</b>	<b>306</b>

**APPENDIX B**  
**INTERVIEWING FLOW CHART**

**Appendix B: Interviewing Flow Chart**



**APPENDIX C**  
**QUESTIONNAIRES**



**Q1.0 Introduction**

Hello, my name is (NAME) representing Advanced Analytics, Inc., a national marketing research firm. Today, we are talking to people like yourself and would like to ask you a few questions.

**Q1.25 Primary Language**

First, what is the primary, that is, main language spoken in your home? (**Do not read list**)

English ..... 1 → (**Skip to Q1.75**)

Another language ..... 2 → (**Ask Q1.5**)

*If respondent does not understand question, terminate and record below.*

**Terminate Q1.25: Does Not Understand Question**  
01 02 03 04 05 06 07 08 09 10 11 12 13 14 15 16 17 18 19 20 (10,11)

**Q1.5 Whether Comfortable Being Interviewed In English**

Are you comfortable being interviewed in English?

Yes..... 1 → (**Continue**)

No ..... 

2
3

 → (**Terminate and record below in appropriate box.**)

Refused.....

*If respondent does not understand question, terminate and record below in appropriate box.*

**Terminate Q1.5: Does Not Understand Question**  
01 02 03 04 05 06 07 08 09 10 11 12 13 14 15 16 17 18 19 20 (12,13)

**Terminate Q1.5: Not Comfortable Being Interviewed In English**  
01 02 03 04 05 06 07 08 09 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25  
26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 (14,15)

**Q2.0 Security**

Do you or any immediate family members work for ... (Read list. Record all mentions)?

- |   |   |                                |
|---|---|--------------------------------|
| An advertising agency .....   | 1 | → (Terminate/<br>record below) |
| A market research company.....  | 2 |                                |
| A package design company.....   | 3 |                                |
| A TV or radio station.....  | 4 |                                |
| A public relations firm .....   | 5 |                                |
| A manufacturer, wholesaler, retailer or distributor<br>of drugs or pharmaceutical products..... | 6 |                                |
| A doctor, nurse, pharmacist or other health<br>care professional.....                           | 7 |                                |
| The Food and Drug Administration.....   | 8 |                                |
| (Do <u>Not</u> Read) → None of these.....   | X | → (Continue)                   |

<b>Terminate Q2.0: Security</b>	01 02 03 04 05 06 07 08 09 10 11 12 13 14 15 16 17 18 19 20	(16, 17)
---------------------------------	---	----------

**Q3.0 Medical Screen**

Are you or any immediate family members... (Read list. Record all mentions)?

- |  |   |                                   |
|--|---|-----------------------------------|
| A doctor/physician .....                             | 1 | → (Terminate and<br>record below) |
| A nurse/registered nurse .....                       | 2 |                                   |
| A medical or nursing student.....                    | 3 |                                   |
| A dentist.....                                       | 4 |                                   |
| A pharmacist .....                                   | 5 |                                   |
| Some other type of health care professional          | 6 |                                   |
| A student in a health care profession or field ..... | 7 | → (Continue)                      |
| (Do <u>Not</u> Read) → None of these.....            | X |                                   |

<b>Terminate Q3.0 Medical Knowledge</b>	01 02 03 04 05 06 07 08 09 10 11 12 13 14 15 16 17 18 19 20	(18, 19)
---	---	----------

**Q4.0 Past Participation**

When was the last time you participated in a market research study, other than a political poll?  
(Do not read list. Record one answer only.)

- |                                     |   |                                   |
|-------------------------------------|---|-----------------------------------|
| Within the past 3 months .....      | 1 | → (Terminate and<br>record below) |
| Longer than 3 months ago/never..... | 2 | → (Continue)                      |

<b>Terminate Q4.0: Past 3 Months Participation</b>	01 02 03 04 05 06 07 08 09 10 11 12 13 14 15 16 17 18 19 20	(20, 21)
--	---	----------

**Q5.0 Age**

Which of the following categories includes your age? *(Read list)*

- |                                      |      |   |   |
|--------------------------------------|------|---|---|
|                                      | (22) |   |   |
| Under 18 .....                       | 0    | → | <i>(Terminate and record below)</i>   |
| 18 to 24 .....                       | 1    |   |   |
| 25 to 34 .....                       | 2    | → | <i>(Check age quotas before continuing. 50% of respondents should be aged 50 or older.)</i> |
| 35 to 49 .....                       | 3    |   |   |
| 50 to 64 .....                       | 4    |   |   |
| 65 or older .....                    | 5    |   |   |
| <i>(Do Not Read)</i> -> Refused..... | 8    | → | <i>(Terminate and record below)</i>   |

<b>Terminate Q5.0: Under 18 / Refused Over Quota Age</b>																			
01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	20

(23,24)

**Q5.5 Gender**

**Record respondent gender here:**

- |              |      |
|--------------|------|
|              | (25) |
| Male .....   | 1    |
| Female ..... | 2    |

**Q6.0 Non-Prescription Products Taken in Past Six Months**

Which, if any, of the following non-prescription products have you yourself used in the past six months? *(Read list beginning at X.. Record all "yes" mentions.)*

- |  |      |
|--|------|
| <b>Start Here</b>                          | (26) |
| ( ) Antacids in tablet or liquid form..... | 1    |
| ( ) Athlete's foot creams or ointments..   | 2    |
| ( ) Pain relievers or analgesics.....      | 3    |
| <b>Read last</b>                           |      |
| None of these .....                        | 9    |

*(Pain relievers or analgesics must be circled to continue. Otherwise, terminate and record in box below.)*

<b>Terminate Q6.0: No Pain Relievers or Analgesics</b>																			
01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	20

(27, 28)

**Q6.5 Brands Taken in Past Six Months**

Which, if any, of the following brands of pain relievers or analgesics have you yourself taken in the past six months? *(Read list beginning at X. Record all "yes" mentions.)*

- Start Here** (29)
- ( ) Tylenol..... 1
  - ( ) Bayer Aspirin..... 2
  - ( ) Advil ..... 3
- Read last** None of these..... 9

*(Advil must be circled to continue. Otherwise, terminate and record in box below.)*

<b>Terminate Q6.5: No Advil</b>																			
01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	20

(30, 31)

**Q6.8 Verification of Advil Use**

You mentioned that you have taken Advil in the past six months. Did the package say Advil, or was it a generic or store brand version of Advil? *(Do not read list. Record all "yes" mentions.)*

- Advil ..... 1
- Store brand/generic version..... 2
- Don't know ..... 3

*(Advil must be circled to continue. Otherwise, terminate and record in box below.)*

<b>Terminate Q6.8: Store brand/generic Advil only/don't know</b>																			
01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	20

(32, 33)

**Q7.0 Reading Glasses/Contact Lenses**

Do you normally wear glasses or contact lenses for reading?

- Yes..... 1 → *(Ask Q7.5)*
- No ..... 2 → *(Skip to Q8.0)*

**Q7.5 Whether Have Glasses/Contact Lenses With Them**

Do you have these glasses or contact lenses with you now?

- Yes..... 1 → *(Ask Q8.0)*
- No ..... 2 → *(Terminate and record below.)*

<b>Terminate Q7.5: No Glasses</b>																			
01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	20

(34, 35)

**(Ask Everyone)**

**Q8.0 Invitation to Participate**

We are conducting a market research study and would like to include you in our survey. The interview will take about 20 minutes. To show our appreciation, we will give you a cash gift at the end of the interview. Are you willing to participate?

- Yes..... 1 → *(Continue to Main Questionnaire)*
- No ..... 2 → *(Terminate and record below)*

<b>Qualified Refusal</b>																			
01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	20

(36, 37)

**Q9.0 REALM Test**

When respondent is at facility, administer REALM test and record score here:

\_\_\_\_\_ (38, 39)

40-79Z
80 - 1

**Advil Label Comprehension Study**  
**- Main Questionnaire -**

CARD 2

[PRINT:]  
 RESPONDENT'S FULL NAME: \_\_\_\_\_

MARKET:		
(5)	(6)	(7)
Akron..... 1	Los Angeles ..... 1	San Francisco ..... 1
Baltimore ..... 2	Massapequa ..... 2	Santa Fe ..... 2
Boston ..... 3	Memphis ..... 3	Seattle ..... 3
Chicago ..... 4	Milwaukee ..... 4	Tucson ..... 4
Cleveland ..... 5	Nashville ..... 5	Woodbridge, NJ..... 5
Detroit..... 6	New Orleans ..... 6	
Ft. Lauderdale ..... 7	Philadelphia ..... 7	
Hartford, CT..... 8	Phoenix..... 8	
Houston..... 9	Rochester ..... 9	
Kansas City ..... 0	San Diego..... 0	

**YOU MUST USE A BLACK PEN TO FILL OUT THIS QUESTIONNAIRE**

**YOU MUST PRINT CLEARLY AND LEGIBLY**

**Q1.0 Exposure to Package**

Now I'd like to hand to you a package for a non-prescription medicine that you may or may not have seen before. Please take time to read the package carefully. Please refer to the top, front, bottom, sides and back of the package. When you are finished, I'll ask you some detailed questions about it. If you wear glasses for reading, please put them on now.

***Hand package to respondent. Allow respondent as much time as he or she wishes to read the package. You (the interviewer) should "look busy with other work" so as not to rush the respondent to read the label.***

***(Interviewer: After respondent has finished looking at the package, say to respondent:) This is not a memory test. I'm going to ask you a series of questions about what the product does and how to use it. If at any point in the interview you wish to re-read what the package says, please feel free to do so. If you wish, you may also hold onto the package. Again, this is not a memory test so please feel free to refer to the package as much as you would like as you answer my questions.***

CARD 2

**Q1.5 What Does This Product Do (Unaided)**

According to what the package says, what does this product do? Please feel free to refer to the package if you wish. (*Do not read list. Record all mentions. Do not probe.*)

- (8)
- Pain reliever/relieves pain..... 1
- Relieves minor aches and pains ..... 2
- Fever reducer/reduces fever ..... 3
- Specific type of pain/aches mentioned:
- Headaches..... 4
- Common Cold ..... 5
- Toothache ..... 6
- Muscle Aches..... 7
- Backaches ..... 8
- Minor Pain of Arthritis ..... 9
- Menstrual Cramps..... X
- Other (*Specify:*) (9)
- \_\_\_\_\_ 0
- Don't know ..... X

**Q2.0 Whether Product is Appropriate for Respondent**

According to the information on this package (*point to package*) and thinking specifically about your own current medical situation today, as well as your medical history, is this product an appropriate product for you to use if you had pain or fever?

- (10)
- Yes ..... 1 → (*Ask Q3.0*)
- No ..... 2 → (*Skip to Q4.0*)
- (*Do Not Read*) Don't know/ Not sure..... 9

**Q3.0 Need to Ask Doctor**

According to the package information, is it OK for you to use this product without first asking your doctor, or do you need to ask your doctor first before using this product?

- (11)
- OK to use without asking..... 1
- Need to ask doctor first ..... 2
- (*Do Not Read*)-→ Don't know/ Not sure..... 9

**Ask Everyone**

*(Interviewer: Be sure to read Q4.0 slowly and distinctly.)*

**Q4.0 Scenario List (Aided)**

We would like to better understand what the package says to people. Please think of adult men and women who have a minor ache or pain—such as headache, toothache or backache — or fever. Imagine that one of these people asked you about this product (*point to product*). For each of these people I describe, please tell me whether, according to the package label, it's OK for this person to take this product, it's not okay for them to take this product or (*pause*) they need to ask a doctor first before taking this product.

The choices are listed on this card. (*Hand Card 4.0*)

Let's start with (*Read X'd Type Of Person*). According to the package, is it OK for this person to take this product, it's not okay for them to take this product, or they need to ask a doctor first? (*Continue in same manner until other types of people have been asked about.*)

START HERE:	Yes, OK	No, Not OK	Needs to Ask A Doctor First	(Do <u>not</u> read) Don't Know	
[ ] a. The person got a backache last night and they've treated their backache in the past with Advil .....	1	2	3	9	(12)
[ ] b. The person consumes three or more alcoholic drinks per day .....	1	2	3	9	(13)
[ ] c. The person has the common cold but is otherwise in good health.....	1	2	3	9	(14)
[ ] d. The person previously had an allergic reaction to a pain reliever.....	1	2	3	9	(15)
[ ] e. The person is under a doctor's care for an ulcer .....	1	2	3	9	(16)
[ ] f. The person has a toothache but otherwise feels fine .....	1	2	3	9	(17)
[ ] g. The person is allergic to ibuprofen .....	1	2	3	9	(18)
[ ] h. The person is currently taking a <b>prescription</b> medication for high blood pressure .....	1	2	3	9	(19)
[ ] i. The person is currently taking a <b>non-prescription</b> cream for an episode of athlete's foot.....	1	2	3	9	(20)
[ ] j. The last time the person took a pain reliever they developed stomach pain.....	1	2	3	9	(21)
<b>READ LAST:</b>					
k. The person wants to give the product in this box ( <b>POINT TO BOX</b> ) to his 9 year old daughter who has a headache.....	1	2	3	9	(22)

**LEAVE CARD 4.0 IN FRONT OF RESPONDENT.**

(Ask Q5.0-5.4 beginning at "X". Make sure Q5.0-Q5.4 are answered before asking Q5.5.)

START  
HERE:

[ ] Q5.0 Whether Okay To Take With Another Product Containing Ibuprofen

Suppose that a person wanted to take this product along with another product containing ibuprofen. According to what this package says, is it OK for this person to take this product, it's not okay for them to take this product or (pause) do they need to ask a doctor first before taking this product (*point to package*)? (*Do not read list.*)

- (23)
- Okay ..... 1
- Not okay..... 2
- Should ask doctor first. 3
- Don't know ..... 9

[ , ] Q5.1 Whether Okay To Take With Other Pain Relievers

Suppose that a person wanted to take this product along with a tablet of another pain reliever such as Tylenol. According to what this package says, is it OK for this person to take this product, it's not okay for them to take this product or (pause) do they need to ask a doctor first before taking this product (*point to package*)? (*Do not read list.*)

- (24)
- Okay ..... 1
- Not okay..... 2
- Should ask doctor first. 3
- Don't know ..... 9

[ ] Q5.2 Whether Okay To Take With Vitamins

Suppose that a person wanted to take this product and they are **also** taking a vitamin pill on a daily basis. According to what this package says, is it OK for this person to take this product, it's not okay for them to take this product or (pause) do they need to ask a doctor first before taking this product (*point to package*)? (*Do not read list.*)

- (25)
- Okay ..... 1
- Not okay..... 2
- Should ask doctor first. 3
- Don't know ..... 9

CARD 2

[ ] Q5.3 **Whether Okay To Take With Multi-Symptom Cold and Flu Medication Containing a Pain Reliever**

Suppose that a person wanted to take this product and they are also taking a Multi-Symptom cold or flu medication **containing a pain reliever**. According to what this package says, is it OK for this person to take this product, it's not okay for them to take this product or (*pause*) do they need to ask a doctor first before taking this product? (*point to package?*) (**Do not read list.**)

- (26)
- Okay ..... 1
- Not okay..... 2
- Should ask doctor first. 3
- Don't know ..... 9

[ ] Q5.4 **Whether Okay To Take If Woman Has Menstrual Cramps**

Suppose that a woman wanted to take this product for menstrual cramps due to her period. Is it OK for her to take this product, it's not okay for her to take this product or (*pause*) does she need to ask a doctor first before taking this product (*point to package*) for her menstrual cramps? (**Do not read list.**)

- (27)
- Okay ..... 1
- Not okay..... 2
- Should ask doctor first. 3
- Don't know ..... 9

(Take Back Card 4.0)

**Q5.5 Pregnancy Warning**

According to what this package says, if a woman is pregnant or breast feeding, is it okay or not okay for her to take this product without first consulting with a healthcare professional? (**Do not read list.**)

- (28)
- Okay ..... 1
- Not okay/need to consult healthcare professional first..... 2
- Don't know ..... 9

CARD 2

**Q6.0 Scenario List II (Aided)**

Now, I'm going to describe to you different things that a person may or may not experience while taking this product. For each, I'd like to know what the package tells you a person should do if they were taking this product and this happened. Specifically, should the person continue to take this product when needed or **(Pause)** should the person stop taking this product and see a doctor. To help you answer this question, this card lists the possible answers **(HAND CARD 6.0)**. Let's start with **(Read X'd scenario)**. According to the package, should the person continue to take this product when needed or **(Pause)** should the person stop taking this product and see a doctor? **(Continue for other scenarios until all are asked.)**

START HERE:	Scenario	Continue To Take The Product When Needed	Stop Taking Product And See Doctor	(Do Not Read) Don't Know	
a. [ ]	The person develops an allergic reaction to this product.....	1	2	9	(29)
b. [ ]	After taking the one dose of this product, the person's muscle ache got somewhat better.....	1	2	9	(30)
c. [ ]	The person feels he/she needs to take this product for more than ten days.....	1	2	9	(31)
d. [ ]	The person develops stomach pain after using this product.....	1	2	9	(32)
e. [ ]	The person took this product for a leg injury which now has become red and swollen.....	1	2	9	(33)
f. [ ]	The person starts using a non-prescription antibiotic cream for a few days for a minor wound.....	1	2	9	(34)
g. [ ]	The person started using this product last night and their toothache pain subsided somewhat.....	1	2	9	(35)
h. [ ]	The person took this product last night for a fever which today has become worse.....	1	2	9	(36)
i. [ ]	The person developed new or unexpected symptoms after using this product.....	1	2	9	(37)
j. [ ]	The person took this product for a fever for three days and still has a fever.....	1	2	9	(38)
k. [ ]	The person has arthritis pain which they want to treat for three or four days.....	1	2	9	(39)

**(Take Back Card 6.0)**

CARD 2

**Q6.5 Symptoms of Allergy to Ibuprofen**

According to the package, what symptoms might you experience if you were having an allergic reaction to ibuprofen? (*Do not read list.*)

- (43)
- Hives..... 1
- Facial swelling ..... 2
- Asthma or wheezing ..... 3
- Shock..... 4
- Other (*Specify:*)
- \_\_\_\_\_..... 0
- Don't know ..... 9

44-

**Q7.0 Initial Dosing- # of Tablets**

Now, let's talk about directions for use. According to the package, how many tablets of this product should a person initially take? (*Do not read list.*)

- (45)
- One..... 1
- Two..... 2
- One or two ..... 3
- Other (*Specify:*)
- \_\_\_\_\_..... 0
- Don't know ..... 9

46-

**Q7.1 4-6 Hour Dosing**

According to the package, what is the **maximum** number of tablets of this product a person can take within a four to six hour period? (*Do not read list.*)

- (47)
- One..... 1
- Two..... 2
- Other (*Specify:*)
- \_\_\_\_\_..... 0
- Don't know ..... 9

48-

CARD 2

**Q7.3 24 Hour Dosing**

According to the package, what is the **maximum** number of tablets of this product a person should take within a **24 hour** period? (*Do not read list.*)

- (49)
- Six .....6
- Other (*Specify:*)  
\_\_\_\_\_.....0
- Don't know .....9

50-

**Q8.0 Package Readability**

(Hand card 8.0)

Which one of the phrases listed on this card best describes how you feel about the **size of print** on the back of the package ? (*Do not read list. Record one answer.*)

- (51)
- The print was very easy to see.....5
- The print was easy to see .....4
- I could see it but had to strain to see the print..3
- I could make out just a little bit of the print .....2
- I could hardly make out anything at all .....1
- Don't know .....9

**REMOVE PACKAGE AND CARD 8.0 FROM VIEW.**

CARD 2

**Ask Everyone**

A few final questions for classification purposes only ...

**9.0 Whether Under Doctor's Care for Continuing Medical Condition**

Are you currently under a doctor's care for a continuing medical condition? *(Do not read list.)*

(52)

- Yes ..... 1 → *(Ask Q9.5)*
- No ..... 2 → *(Skip to Q9.8)*
- Don't know / refused..... 9

**9.5 Continuing Medical Condition**

For which specific continuing medical condition or conditions do you see or consult with a doctor? *(Record response verbatim.)*

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53-  
54-  
55-  
56-

*(Ask Everyone)*

**9.8 Whether Taking Any Drug on a Regular Basis**

Excluding vitamins are you currently taking any prescription or non-prescription drugs on a regular basis? *(Do not read list.)*

(57)

- Yes ..... 1 → *(Ask Q9.9)*
- No ..... 2 → *(Skip to Q10.0)*
- Don't know / refused..... 9

**9.9 Which Drugs Take on a Regular Basis**

Are the drugs you take on a regular basis. . . *(Read list. Record all mentions)*

(58)

- Prescription medications ..... 1
- Non-prescription medications, or..... 2
- Both prescription and non-prescription medications 3
- (Do not read)* Don't know/refused ..... 9

*(Ask everyone)*

**10.0 Whether Ever Had An Allergic Reaction to Any Pain Reliever/Fever Reducer**

Have you ever had an allergic reaction to any pain reliever or fever reducer? *(Do not read list.)*

- (59)
- Yes ..... 1
- No ..... 2
- Don't know/refused ..... 9

**11.0 Whether Ever Had Problems/Side Effects With Pain Relievers/Fever Reducers**

You may or may not have already mentioned this ...Have you ever had problems or side effects with any pain reliever or fever reducer? *(Do not read list.)*

- (60)
- Yes ..... 1
- No ..... 2
- Don't know/refused ..... 9

*(Ask Q12.0 of WOMEN ONLY. Otherwise skip to Q13.0.)*

**12.0 Whether Pregnant/Breast Feeding**

Are you pregnant or breast feeding? *(Do not read list.)*

- (61)
- Yes ..... 1
- No ..... 2
- Don't know/refused ..... 9

*(Ask everyone. Hand card 13.0)*

**Q13.0 Alcoholic Beverage Consumption**

Which letter on this card best describes how many alcoholic drinks you consume in a typical day? *(Do not read list.)*

- (62)
- A. None..... 0
- B. One ..... 1
- C. Two ..... 2
- D. Three or more..... 3
- Don't know/refused ..... 9

*(Take back card 13.0)*

CARD 2

**Q14.0 Doctor recommendation of Advil**

Has your doctor ever recommended that you take Advil? (*Do not read list.*)

(63)

- Yes ..... 1 → (*Ask Q's. 14.1 & 14.2*)
- No ..... 2 → (*Skip to Q14.3*)
- Don't know / refused..... 9

**Q14.1 Recommended # of Tablets Per Dose**

The last time you spoke with your doctor about Advil, how many tablets of Advil per dose did your doctor recommend you take?

(*Do not read list.*)

(64)

- One..... 1
- Two..... 2
- One or two ..... 3
- Three ..... 4
- Other (*Specify:*)  
..... 0
- Doctor did not say.....X
- Don't know..... 9

**Q14.2 Length of Time Recommended Take Advil**

The last time you spoke to your doctor about Advil, for how long a period of time did your doctor recommend you take Advil? (*Record answer in days, weeks or months as stated by the respondent or use one of the other listed responses.*)

# of days: \_\_\_\_\_ # of weeks: \_\_\_\_\_ # of months \_\_\_\_\_  
(65,66) (67,68) (69,70)

(*Do not read*) (71)

- For as long as needed ..... 1
- For a few days ..... 2
- Other (*Specify:*)  
..... 0
- Don't know ..... 9

CARD 2

(Ask everyone)

Q14.3 Advil/Ibuprofen Consultation

You may or may not have already mentioned this... Have you ever asked your doctor whether or not it was OK for you to take Advil or another non-prescription pain reliever or fever reducer that contains ibuprofen? (Do not read list)

- (73)
- Yes ..... 1 → (Ask Q14.4)
- No ..... 2 → (Skip to Q15.0)
- Don't know ..... 3

14.4 Last time asked about Advil

The last time you asked your doctor about Advil or another non-prescription pain reliever or fever reducer that contains Ibuprofen, did the doctor say it was Ok for you to take that type of product or Not Okay for you to take that type of product?

- (74)
- Yes, okay ..... 1
- No, not okay ..... 2
- (Do not read) → Don't know ..... 3

(Ask Everyone)

(Hand Card 15.0)

Q15.0 Race/Ethnicity

Which letter on this card best describes your ethnic or racial background? (Read list if necessary.)

- (75)
- A. African-American/Black ..... 1
- B. American Indian..... 2
- C. Asian ..... 3
- D. Hispanic/Latino..... 4
- E. White/Caucasian ..... 5
- F. Other ..... 6
- (Do Not Read) → Refused ..... Y

(Take Back Card 15.0)

76-79Z | 80-2

- Thank respondent.
- Ask respondent to sign and date Certification on next page.
- Read, sign and date Certification on next page.
- Make sure respondent's name is on front of Screener, Main Questionnaire and REALM Test.

**CERTIFICATION PAGE**

**Respondent**

I certify that I am 18 years of age or older, and that I was asked a series of questions about a package I was shown.

RESPONDENT'S SIGNATURE: \_\_\_\_\_

DATE:            \_\_\_\_\_ /            /    02

**Interviewer**

I certify that I carried out this interview in accordance with my interviewer's instructions and supervisor's briefing.

INTERVIEWER'S SIGNATURE: \_\_\_\_\_

DATE:            \_\_\_\_\_ /            /    02

**APPENDIX D**  
**THE REALM TEST**

# RAPID ESTIMATE OF ADULT LITERACY IN MEDICINE (REALM) Examiner's Instruction Sheet

Terry Davis, PhD, Michael Crouch, MN, Sandy Long, PhD

The Rapid Estimate of Adult Literacy in Medicine (REALM) is a screening instrument to assess an adult patient's ability to read common medical words and lay terms for body parts and illnesses. It is designed to assist medical professionals in estimating a patient's literacy level so that the appropriate level of patient education materials or oral instructions may be used. The test takes two to three minutes to administer and score. The REALM has been correlated with other standardized tests (Family Medicine, 1993: 25:391-5).

**Directions to the Examiner:**

1. Examiner should say to the patient:  
*"This survey is to help us figure out the best type of patient education materials to give you. The survey only takes 2 to 3 minutes to do"*
2. Give the patient a laminated copy of the "REALM" Patient Word List.
3. Examiner should hold an unlaminated "REALM" Score Sheet on a clipboard at an angle so that the patient is not distracted by your scoring procedure.
4. Examiner should say:  
*"I want to hear you read as many words as you can from this list. Begin with the first word on List 1 and read aloud. When you come to a word you cannot read, do the best you can or say "blank" and go on to the next word."*
5. If the patient takes more than five seconds on a word say "blank" and point to the next word, if necessary, to move the patient along. If the patient begins to miss every word; have him/her pronounce only known words.
6. Count as an error any word not attempted or mispronounced. Score by:
  - ◆ (/) after each mispronounced word.
  - ◆ (-) after each word not attempted.
  - ◆ (+) after each word pronounced correctly.
7. Count the number of correct words for each list and record the numbers in the "SCORE box. Total the numbers and match the total score with its grade equivalent in the table below.
8. Record the "Realm" generated reading level on the Examiner's Score Sheet and in the Education/Learning History section of the Social and Patient Education History assessment form in the Medical Record.

Raw Score	Grade Range	Description
0-18	3 <sup>rd</sup> Grade and Below	Will not be able to read most low literacy materials; will need repeated oral instructions; materials composed primarily of illustrations or audio or video aids.
19-44	4 <sup>th</sup> to 6 <sup>th</sup> Grade	Will need low literacy materials; may not be able to read prescription labels.
45-60	7 <sup>th</sup> to 8 <sup>th</sup> Grade	Will struggle with most patient education materials.
61-66	High School	Will be able to read most patient education materials.

Red Lake Hospital  
Red Lake, MN 56671  
4/98/34cD

<b>fat</b>	<b>fatigue</b>	<b>allergic</b>
<b>flu</b>	<b>pelvic</b>	<b>menstrual</b>
<b>pill</b>	<b>jaundice</b>	<b>testicle</b>
<b>dose</b>	<b>infection</b>	<b>colitis</b>
<b>eye</b>	<b>exercise</b>	<b>emergency</b>
<b>stress</b>	<b>behavior</b>	<b>medication</b>
<b>smear</b>	<b>prescription</b>	<b>occupation</b>
<b>nerves</b>	<b>notify</b>	<b>sexually</b>
<b>germs</b>	<b>gallbladder</b>	<b>alcoholism</b>
<b>meals</b>	<b>calories</b>	<b>irritation</b>
<b>disease</b>	<b>depression</b>	<b>constipation</b>
<b>cancer</b>	<b>miscarriage</b>	<b>gonorrhea</b>
<b>caffeine</b>	<b>pregnancy</b>	<b>inflammatory</b>
<b>attack</b>	<b>arthritis</b>	<b>diabetes</b>
<b>kidney</b>	<b>nutrition</b>	<b>hepatitis</b>
<b>hormones</b>	<b>menopause</b>	<b>antibiotics</b>
<b>herpes</b>	<b>appendix</b>	<b>diagnosis</b>
<b>seizure</b>	<b>abnormal</b>	<b>potassium</b>
<b>bowel</b>	<b>sypilis</b>	<b>anemia</b>
<b>asthma</b>	<b>hemorrhoids</b>	<b>obesity</b>
<b>rectal</b>	<b>nausea</b>	<b>osteoporosis</b>
<b>incest</b>	<b>directed</b>	<b>impetigo</b>

**RAPID ENTRY ANAMNOSIS**  
(REALM)

Terry Davis, PhD, Michael Cronch, MD, Sandy Long, PhD

**Class:** \_\_\_\_\_

**Room:** \_\_\_\_\_

**Name:** \_\_\_\_\_

**DOB:** \_\_\_\_\_

**REALM generated reading level:** \_\_\_\_\_

**Grade:** \_\_\_\_\_

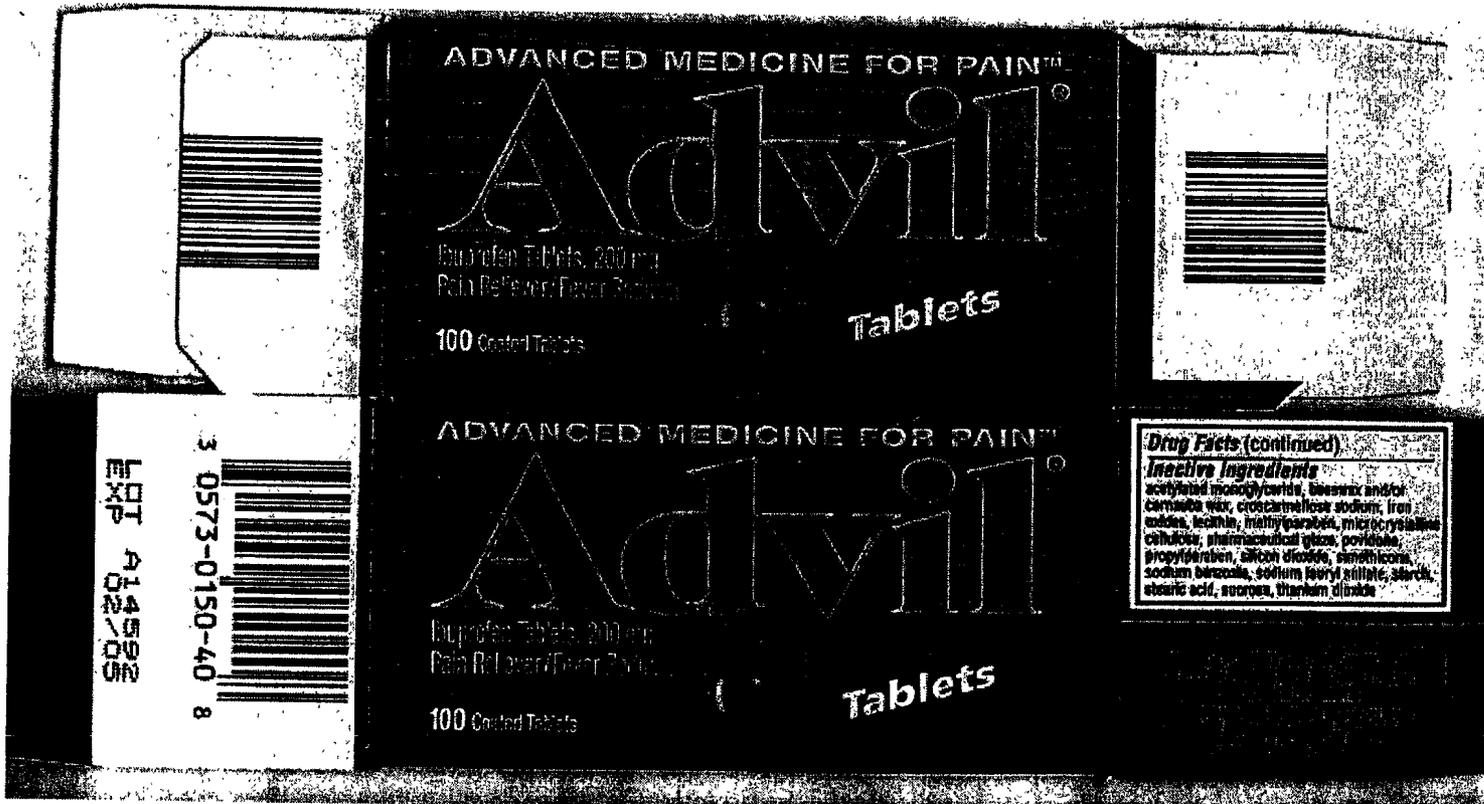
List 1		List 2		List 3	
Fat	_____	Fatigue	_____	Allergic	_____
Flu	_____	Pelvic	_____	Menstrual	_____
Pill	_____	Jaundice	_____	Testicle	_____
Dose	_____	Infection	_____	Colitis	_____
Eye	_____	Exercise	_____	Emergency	_____
Stress	_____	Behavior	_____	Medication	_____
Smear	_____	Prescription	_____	Occupation	_____
Nerves	_____	Notify	_____	Sexually	_____
Germ	_____	Gallbladder	_____	Alcoholism	_____
Meals	_____	Calories	_____	Irritation	_____
Disease	_____	Depression	_____	Constipation	_____
Cancer	_____	Miscarriage	_____	Gonorrhea	_____
Caffeine	_____	Pregnancy	_____	Inflammatory	_____
Attack	_____	Arthritis	_____	Diabetes	_____
Kidney	_____	Nutrition	_____	Hepatitis	_____
Hormones	_____	Menopause	_____	Antibiotics	_____
Herpes	_____	Appendix	_____	Diagnosis	_____
Seizure	_____	Abnormal	_____	Potassium	_____
Bowel	_____	Syphilis	_____	Anemia	_____
Asthma	_____	Hemorrhoids	_____	Obesity	_____
Rectal	_____	Nausea	_____	Osteoporosis	_____
Incest	_____	Directed	_____	Impetigo	_____
# of (+) Responses in List 1: _____		# of (+) Responses in List 2: _____		# of (+) Responses in List 3: _____	

**LEGEND:** (+) Current, (-) Past, (0) None

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4/98/IMcD

**APPENDIX E**  
**ADVIL CARTON LABEL**



ADVANCED MEDICINE FOR PAIN™

Advill®

Ibuprofen Tablets, 200 mg  
Pain Reliever/Fever Reducer

100 Coated Tablets

Tablets

ADVANCED MEDICINE FOR PAIN™

Advill®

Ibuprofen Tablets, 200 mg  
Pain Reliever/Fever Reducer

100 Coated Tablets

Tablets

**Drug Facts (continued)**  
**Inactive Ingredients**  
acetylated monoglycerol, beeswax and/or  
carnauba wax, croscarmellose sodium, iron  
oxides, lactin, methylparaben, microcrystalline  
cellulose, pharmaceutical glaze, polydioxane,  
propylparaben, silicon dioxide, stearic acid,  
sodium bicarbonate, sodium lauryl sulfate, starch,  
stearic acid, sucrose, titanium dioxide

LOT 4145925  
EXP 02/05

3 0573-0150-40 8

**Drug Facts**

**Active Ingredient  
(in each tablet)**

Ibuprofen 200 mg.....Pain reliever/fever reducer

**Purposes**

**Uses**

- in temporarily relieves minor aches and pains due to:
  - in headache
  - in the common cold
  - in toothache
  - in muscular aches
  - in temporarily reduces fever
- in backache
- in minor pain of arthritis
- in menstrual cramps

**Warnings**

Allergy alert: Ibuprofen may cause a severe allergic reaction which may include:

- in hives
- in facial swelling
- in asthma (wheezing)
- in shock

**Drug Facts (continued)**

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

**Do not use if you have ever had an allergic reaction to any other pain reliever/fever reducer**

**Ask a doctor before use if you have had problems or side effects with any pain reliever/fever reducer**

**Ask a doctor or pharmacist before use if you are under a doctor's care for any continuing medical condition**

**in taking other drugs on a regular basis**  
**in taking any other product containing ibuprofen, or any other pain reliever/fever reducer**

**Drug Facts (continued)**

**Stop use and ask a doctor if**

- in an allergic reaction occurs. Seek medical help right away.
- in fever gets worse or lasts more than 3 days
- in pain gets worse or lasts more than 10 days
- in stomach pain occurs with the use of this product
- in the painful area is red or swollen
- in any new or unexpected symptoms occur

**If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use ibuprofen 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.**

**Drug Facts (continued)**

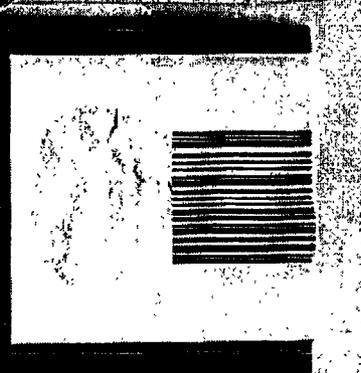
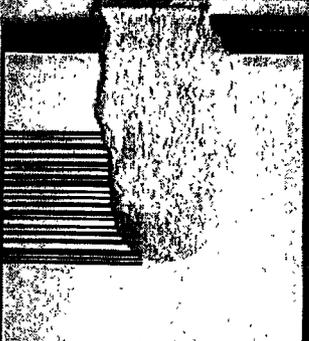
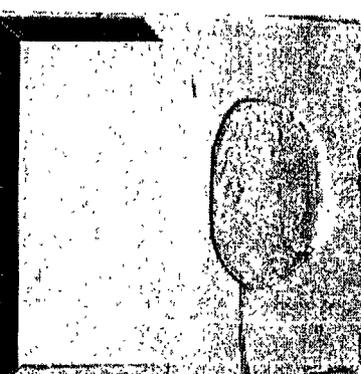
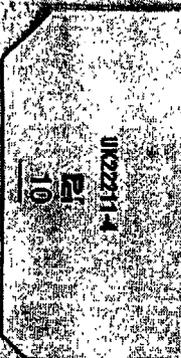
**Directions**

**in Do not take more than directed**  
**in adults: take 1 tablet every 4 to 6 hours while symptoms occur**

**in If pain or fever does not respond to 1 tablet, 2 tablets may be used; but do not exceed 6 tablets in 24 hours, unless directed by a doctor**  
**in the smallest effective dose should be used**  
**in children: do not give to children under 12 unless directed by a doctor**

**Other information**

**in read all warnings and directions before use. Keep carton.**  
**in store at 20-25°C (68-77°F)**  
**in avoid excessive heat 40°C (above 104°F)**



**APPENDIX F**  
**VALIDATION REPORT**

## Outfielders, Inc.

---

Frances Murray Tavolilla  
100 North Road  
Eastchester NY, 10709  
(914) 961-8042

September 24, 2002

Ms. Nelly Valentin  
Advanced Analytics  
3 West 35th Street  
New York, NY 10001

Dear Nelly,

The validation results of your Advil Label Comprehension Study #MA11-012 are as follows:

Out of the 306 listed respondent names, 301 gave telephone numbers. Of these, 147 were successfully contacted (49%). Of those not reached, a minimum of three attempts were made on different days of the week and at different times of the day.

Of those contacted, there were no discrepancies found in interviewing procedures. All results of this phase of the study were reported to Advanced Analytics.

If you have any questions regarding this study, please call me.

Sincerely,

*Frances M. Tavolilla*

Frances Murray Tavolilla

### VALIDATION QUESTIONNAIRE

- ASK TO SPEAK TO THE PERSON WHOSE NAME IS LISTED ON VALIDATION SHEET
- CORRECT ANSWERS ARE CIRCLED
- PROBE WHERE INDICATED

Hello (Mr, Mrs, Miss.) \_\_\_\_\_, I'm from Advanced Analytics in New York. Recently a study was done in your area and we're calling to thank you for your participation and to confirm a few points.

1. Recently, did you take part in a survey at the mall where you were shown a package for a non-prescription medicine and asked some questions about it?

YES.....  1

NO ..... 2 → *(Before terminating, be sure no one else in household was interviewed)*

2. Which of the following includes your age?

Under 18 years ..... 1

18 - 34.....  2

35 - 49.....  3

50+.....  4

→ *(Check against validation listing)*

3. Have you taken a non-prescription pain reliever or analgesic within the past six months?

Yes.....  1

No ..... 2

→ *Must mention to qualify*

4. Have you taken Advil within the past six months?

Yes.....  1

No ..... 2

→ *Must mention to qualify*

Thank respondent.

**APPENDIX G**  
**CURRICULUM VITAE OF MORRIS S. WHITCUP, Pd.D.**

## **Curriculum Vitae Of Morris S. Whitcup, Ph.D.**

### **OVERVIEW**

Morris S. Whitcup, Ph.D. is founder and president of Advanced Analytics, Inc., a marketing research and consulting firm located in New York City. Dr. Whitcup has nearly 25 years experience in survey and marketing research.

Since receiving his Ph.D. in Social Psychology from Columbia University, Dr. Whitcup has held senior executive positions with several research and consulting firms, including AHF/Macro, Guideline Research Corporation, Lieberman Research, Custom Research, Inc., and Cooper and Company. Dr. Whitcup has extensive experience in pharmaceuticals, consumer packaged goods, health, beauty aids and fragrances.

Dr. Whitcup has been recognized as an expert witness in marketing research in several court jurisdictions and has appeared before the NAD (the National Advertising Division of the Council of Better Business Bureaus, Inc.) and NARB (their appeals board) as an expert witness in the fields of advertising communication and miscommunication. He has also authored several major technical reports published by the U.S. Government for the Departments of Health, Defense and Social Security Administration.

Dr. Whitcup estimates that in the course of his career he has participated in the design and analysis of over 2,500 market and survey research studies.

### **EDUCATION**

Ph.D., Columbia University, May, 1977 in the field of Social Psychology  
B.A., Yeshiva College, Summa Cum Laude, 1965

### **EMPLOYMENT HISTORY**

President, Advanced Analytics, Inc., 1995 – present  
Vice President, Custom Research Inc., 1994-1995  
Vice President, Guideline Research Corporation, 1985-1994  
Vice President, Lieberman Research, 1984-1985  
Vice President, AHF Marketing Research, 1979 –1984  
Senior Management Scientist, Cooper and Company, 1975- 1980

**Dissertation**

"An Investigation into the Effects of Density, Aggregate Number and Anonymity Upon Conformity and Aggression," Columbia University, 1977

**PROFESSIONAL ARTICLES**

"Ten Rules to Follow in Warning Label Comprehension Research," Whitcup, M., *1999 Annual CASRO Journal*, 169-172.

"Field and Laboratory Studies of Littering," Krause, R.M., Freedman, J.L., and Whitcup, M., *Journal of Experimental Social Psychology*, 14, 109-112, 1978.

**U.S. GOVERNMENT REPORTS**

"Development and Design of a Social Services Voucher System," *Social and Rehabilitation Service, U.S. Department of Health, Education and Welfare, September, 1977 (with Cooper, G., Katz, A.)*

"A Survey of Foundations Involved In U.S. Health R&D," U.S. Department of Health, Education and Welfare, National Institutes of Health, January, 1978 (with Samers, B. N. and Kelly, D. I.)

"Improvement of Interviewing in SS Claims Processes," *Social Security Administration, April, 1979 (with Cooper, G.)*

"The Cost and Value of Military Health Care Benefits," *Office of the Assistant Secretary of Defense (Health Affairs), May, 1979 (with Samers, B. N. and Lenz, P. R.)*

"Comparative Learning Styles in Alternative Modes of Continuing Education," *National Science Foundation, Division of Science Education and Research, September, 1979 (with Samers, B. N.)*

**APPENDIX H**

**NUMBER OF INTERVIEWS COMPLETED IN EACH INTERVIEWING SITE**

NUMBER OF INTERVIEWS COMPLETED IN EACH INTERVIEWING SITE

	<u>Total</u> #
1. Akron, OH	12
2. Baltimore, MD	12
3. Boston, MA	12
4. Chicago, IL	12
5. Cleveland, OH	12
6. Detroit, MI	12
7. Ft. Lauderdale, FL	16
8. Hartford, CT	12
9. Houston, TX	12
10. Kansas City, KS	12
11. Los Angeles, CA	14
12. Massapequa, NY	12
13. Memphis, TN	12
14. Milwaukee, WI	12
15. Nashville, TN	8
16. New Orleans, LA	12
17. Philadelphia, PA	13
18. Phoenix, AZ	9
19. Rochester, NY	12
20. San Diego, CA	16
21. San Francisco, CA	12
22. Santa Fe, NM	14
23. Seattle, WA	12
24. Tucson, AZ	12
25. Woodbridge, NJ	12
<b>Total</b>	<b>306</b>

**APPENDIX I**  
**CATEGORIZATION OF CORRECT AND INCORRECT RESPONSES**

**Q1.5 What Does this Product Do (Unaided)\***

Responses relating to pain relief, fever reducer or specific types of pain	Correct
All other responses	Incorrect

**\* To be counted as giving a Correct overall answer to this question, respondent must provide at least one Correct response and no Incorrect responses**

**Q2.0 / 3.0 Whether Product Is Appropriate for Respondent (Selection/Deselection)\***

<b><u>Respondent's Designation:</u></b>	<b><u>Okay To Use Without Asking</u></b>	<b><u>Need To Ask Doctor First</u></b>	<b><u>Not Appropriate To Use</u></b>	<b><u>Don't Know</u></b>
Need to consult	Incorrect	Preferred	Acceptable	Incorrect
No need to consult	Preferred	Acceptable	Incorrect	Incorrect
Allergic to pain relievers	Incorrect	Acceptable	Preferred	Incorrect

**\*For this question, Correct responses will be those coded as either Preferred or Acceptable**

**Q4.0 Scenario List I (Aided)\***

<b><u>TYPE OF PERSON</u></b>	<b><u>Yes, Okay</u></b>	<b><u>No, Not Okay</u></b>	<b><u>Needs To Ask A Doctor First</u></b>	<b><u>Don't Know</u></b>
a. The person got a backache last night and they've treated their backache in the past with Advil	Preferred	Incorrect	Acceptable	Incorrect
b. The person consumes three or more alcoholic drinks per day	Incorrect	Acceptable	Preferred	Incorrect
c. The person has the common cold but is otherwise in good health	Preferred	Incorrect	Acceptable	Incorrect
d. The person previously had an allergic reaction to a pain reliever	Incorrect	Preferred	Acceptable	Incorrect
e. The person is under a doctor's care for an ulcer	Incorrect	Acceptable	Preferred	Incorrect
f. The person has a toothache but otherwise feels fine	Preferred	Incorrect	Acceptable	Incorrect
g. The person is allergic to ibuprofen	Incorrect	Preferred	Acceptable	Incorrect
h. The person is currently taking a prescription medication for high blood pressure	Incorrect	Acceptable	Preferred	Incorrect
i. The person is currently taking a <u>non</u> -prescription cream for an episode of athlete's foot	Preferred	Incorrect	Acceptable	Incorrect
j. The last time the person took a pain reliever they developed stomach pain	Incorrect	Acceptable	Preferred	Incorrect
k. The person wants to give the product in this box to his 9 year old daughter who has a headache	Incorrect	Acceptable	Preferred	Incorrect

**\*For this question, Correct responses will be those coded as either Preferred or Acceptable**

**Q5.0 Take With Another Product Containing Ibuprofen\***

Okay  
Not okay  
Should ask doctor first  
Don't know

Incorrect  
Acceptable  
Preferred  
Incorrect

**Q5.1 Take With Other Pain Relievers\***

Okay  
Not okay  
Should ask doctor first  
Don't know

Incorrect  
Acceptable  
Preferred  
Incorrect

**Q5.2 Take With Vitamins\***

Okay  
Not okay  
Should ask doctor first  
Don't know

Preferred  
Incorrect  
Acceptable  
Incorrect

**\*For this question, Correct responses will be those coded as either Preferred or Acceptable**

**Q5.3 Take With Multi-Symptom Cold  
And Flu Medication Containing a Pain Reliever\***

Okay  
Not okay  
Should ask doctor first  
Don't know

Incorrect  
Acceptable  
Preferred  
Incorrect

**Q5.4 Take If A Woman Has Menstrual Cramps\***

Okay  
Not okay  
Should ask doctor first  
Don't know

Preferred  
Incorrect  
Acceptable  
Incorrect

**Q5.5 Take If A Woman Is Pregnant Or Breast Feeding**

Okay  
Not okay / need to consult healthcare professional first  
Don't know

Incorrect  
Correct  
Incorrect

**\*For this question, Correct responses will be those coded as either Preferred or Acceptable**

**Q6.0 Scenario List II (Aided)**

<b><u>TYPE OF PERSON</u></b>	<b><u>Continue To Take The Product When Needed</u></b>	<b><u>Stop Taking Product And See Doctor</u></b>	<b><u>Don't Know</u></b>
a. The person develops an allergic reaction to this product	Incorrect	Correct	Incorrect
b. After taking the one dose of this product, the person's muscle ache got somewhat better	Correct	Incorrect	Incorrect
c. The person feels he / she needs to take this product for more than ten days	Incorrect	Correct	Incorrect
d. The person develops stomach pain after using this product	Incorrect	Correct	Incorrect
e. The person took this product for a leg injury which now has become red and swollen	Incorrect	Correct	Incorrect
f. The person starts using a non-prescription antibiotic cream for a few days for a minor wound	Correct	Incorrect	Incorrect
g. The person started using this product last night and their toothache pain subsided somewhat	Correct	Incorrect	Incorrect
h. The person took this product last night for a fever which today has become worse	Incorrect	Correct	Incorrect
i. The person developed new or unexpected symptoms after using this product	Incorrect	Correct	Incorrect
j. The person took this product for a fever for three days and still has a fever	Incorrect	Correct	Incorrect
k. The person has arthritis pain which they want to treat for three or four days	Correct	Incorrect	Incorrect

**Q6.5 What Symptoms Might Occur As A Result  
Of An Allergic Reaction To Ibuprofen\***

Hives	Correct
Facial swelling	Correct
Asthma or wheezing	Correct
Shock	Correct
“Other” responses which can be classified as hives, facial swelling, asthma / wheezing or shock	Incorrect
* To be counted as giving a Correct overall answer to this question, respondent must provide at least one Correct response and no Incorrect responses	

**Q7.0 How Many Tablets To Initially Take**

One	Correct
Two	Correct
One or two	Correct
All other responses	Incorrect

**Q7.1 Maximum Number Of Tablets Can Take Within Four To Six Hour Period\***

One	Acceptable
Two	Preferred
All other responses	Incorrect

\* For this question, Correct responses will be those coded as either Preferred or Acceptable

**Q7.3 Maximum Number Of Tablets Should Take  
Within Twenty-Four Hour Period\***

Six  
Responses from one to five  
All other responses

Preferred  
Acceptable  
Incorrect

\* For this question, Correct responses will be those coded as either Preferred or Acceptable

**Q8.0 Package Readability**

Not classified; for informational purposes only

**Q9.0-15.0 For Classification Purposes Only**



This report was prepared by James D. Lewis, MD, MSCE at the request of Wyeth Consumer Healthcare. Specifically, I was asked to review the following manuscript and to provide a critique of the methods used in the study:

Blot WJ, McLaughlin JK. Over the counter non-steroidal anti-inflammatory drugs and risk of gastrointestinal bleeding. *J Epidemiol Biostat* 2000;5:137-42.

The study is a case-control study based on data collected by a survey of members of the American College of Gastroenterology. The survey was conducted from May 1995 to August 1995. The purpose of the original survey, as described in the original publication<sup>1</sup>, was as a "pilot project intended to determine the feasibility of surveying ACG members and Fellows about common clinical issues..."

The design of the survey was relatively simple. Members and Fellows were asked to complete the survey for up to 10 bleeding patients and for 10 procedure-matched controls. The procedure-matched control was to be the next patient (either inpatient or outpatient) having the same procedure as the case subject. The submitted data were assumed to be accurate and were used as recorded.

The survey collected data on demographic information such as age, sex, tobacco use, alcohol use, and medication use, site of bleeding, management, and outcome. The authors concluded from analysis of the data that use of OTC NSAIDs was associated with an increased risk of gastrointestinal bleeding.

There are several potential flaws to the Blot study<sup>2</sup>, each of which will be discussed in detail.

### **Selection bias**

Case-control studies are subject to selection bias if selection of cases or controls is in any way related to the exposure of interest. This study was potentially subject to selection bias for both cases and controls.

### **Selection of controls**

Understanding the possible selection bias among controls is quite simple. Control subjects were selected from sequential patients undergoing the same endoscopic procedure as case patients. By definition, the control subjects must have been symptomatic patients, thereby justifying the upper endoscopy or colonoscopy. Evidence to this is the high prevalence of esophagitis among control subjects (19.6%)<sup>1</sup>. Patients with symptoms are likely to avoid NSAIDs, either based on their own experience or at

the recommendation of their physician. Although the investigators reported to have adjusted for the prevalence of dyspeptic symptoms, it is unclear how well this adjustment can account for this potential selection bias.

Likewise, for patients undergoing elective procedures, many gastroenterologists routinely recommend discontinuation of all aspirin and NSAIDs for a minimum of one week prior to the procedure. This would result in a substantial reduction in the prevalence of NSAID use in the controls.

Thus, there is ample evidence that this study could be subject to selection bias related to the selection of controls. This bias would result in selecting a cohort of control subjects with low use of NSAIDs. Careful examination of the data provides evidence that such bias may have occurred. Consumption of NSAIDs (either prescription or OTC) was reported by only 22% of controls. This is lower than expected based on other studies. For example, in the Slone Survey<sup>3</sup>, a recent population-based survey of non-institutionalized US residents using random digit dialing the apparent rates of use were much higher. In that study, respondents reported use of medications in the prior week. Among persons 45 and older (i.e., comparable to the subjects in the Blot study), 7% to 22% used ibuprofen, 21% to 39% used aspirin, and 3% to 4% used naproxen. The total OTC NSAID use reported for controls in the Blot study was only 17.5% and any NSAID use among controls was only 22.0%. These rates of use seem very low based on the results of the Slone Survey<sup>3</sup>. This strongly suggests possible selection bias such that controls were selected in a manner that resulted in lower prevalence of NSAID use. Note this could also be a result of information bias which is discussed further below.

#### Selection of cases

Selection bias among case selection is more complicated than among controls. Cases were selected by the practicing physicians. There are no data presented in the original paper describing this project<sup>1</sup> or in the Blot paper<sup>2</sup> describing how the physicians selected which bleeding patients to include in the survey. Furthermore, as is noted in the original paper, there was no data on how many patients were submitted by any individual physician. Thus, it is very possible that many physicians submitted only a few cases and that these cases were likely more severely ill. These severely ill patients may have triggered the physician to remember to complete the survey.

Evidence to this is the severity of illness of the cases. Looking at the cases with upper GI bleeding, who represent 76% of the case subjects<sup>1</sup>, 35% presented with orthostasis or shock, 64% received transfusions, and 51% received endoscopic therapy. The high rate of endoscopic therapy is particularly interesting given the endoscopic findings. 99 (21%) of the 482 patients with upper GI bleeding had only esophagitis or gastric erosions identified<sup>1</sup>. Thus, these patients would not have been candidates for endoscopic therapy. An additional 6% had Mallory Weiss tears, a condition rarely requiring endoscopic therapy. Therefore, between 21% and 27% of patients had lesions rarely if ever treated with endoscopic therapy. The 51% of patients receiving endoscopic therapy are presumably selected from the remaining 73% to 79% of the cases (or

approximately 64% of the remaining patients receiving endoscopic therapy after excluding patients with only gastric erosions or esophagitis). If we assume that all patients with varices received endoscopic therapy, this translates to 58% of patients with peptic ulcer disease, Mallory Weiss tears, or "other findings" receiving endoscopic therapy. While more detailed information are not provided on these subjects, this appears to be higher than expected if all patients with upper GI bleeding from peptic ulcer disease were included. For example, base on a review on this topic<sup>4</sup>, approximately 16.6% of ulcers would be expected to have a non-bleeding visible vessel and 17.5% to have active bleeding. Thus, it seems plausible that the respondents may have preferentially reported their most severe cases and those most likely to have peptic ulcer disease with stigmata of recent or active hemorrhage.

It is well established that prescription NSAID use increases the risk of peptic ulcer disease and upper GI bleeding. Recognizing the anti-platelet effect of NSAIDs, it is hypothesized that use of high dose NSAIDs would be positively associated with detection of active bleeding or a visible vessel at endoscopy for peptic ulcer disease. Because of the selection process used in this study, the case group may be over represented by the patients taking higher doses of OTC NSAIDs than would be seen if all patients with UGI bleeding were included in the case group (i.e., the cases of upper GI bleeding from peptic ulcer disease are more likely to have active bleeding or visible vessels and therefore may be overly represented by patients taking high doses of NSAIDs and under represented by patients with peptic ulcers secondary to other factors such as H. pylori infection). This would serve to artificially inflate the prevalence of OTC NSAID use in the case group.

#### **Information bias**

There are several forms of information bias that could have affected the results of this study. These are discussed below.

#### **Detection bias**

Detection bias, also referred to as interviewer bias, is a form of information bias. Detection bias can influence the results of case-control studies if case subjects are systematically queried more or less intensely with regards to the exposure data. As previously described, the case subjects may be over represented by subjects that had the most severe peptic ulcers and other sources of GI bleeding. The relevance of this finding is that the physician is also likely to question these patients more closely regarding use of OTC NSAIDs than patients with less severe ulcer disease or less severe bleeding. This could serve to increase the prevalence of reported OTC NSAID use in the case subjects relative to the control subjects. Likewise, if control subjects were evaluated for conditions not routinely recognized to be associated with NSAID use, the physicians may have less rigorously questioned the control patients about their NSAID use.

#### **Recall bias**

Patients admitted to hospital with GI bleeding may be more likely than controls to recall NSAID use, particularly OTC NSAID use. There were no standardized methods employed in this study to increase recall among cases or controls. Lack of this methodology could have profoundly biased the results.

#### Misclassification bias

There were no efforts undertaken in this study to examine the quality of the data collected. The respondents did not undergo any formal training in collecting the data or completing the forms. What affect this design may have had on the results is unknown.

#### Confounding

The authors report that they have adjusted all analyses of OTC NSAIDs for use of prescription NSAIDs and aspirin. This approach may be insufficient for the analyses to account for the true effect of use of OTC NSAIDs. As shown in their dose analyses, there is an apparent dose response curve between NSAIDs and GI bleeding. This has been previously demonstrated by others. It is possible that the authors would have found very different results if they had excluded all cases and controls with prescription NSAID and/or aspirin use. This analysis would give the effect of OTC NSAID use in the absence of these other factors. In fact, the finding of a greater odds ratio for OTC ibuprofen than for prescription NSAIDs (2.4 vs 2.1) suggests that these analyses may have been biased from incomplete control of confounding. Of course, as previously described, this could also be largely related to detection bias and recall bias as well.

#### Conclusions

It is important to note that the authors of the original paper<sup>1</sup> as well as the Blot paper<sup>2</sup> have both emphasized the importance of viewing these data as hypothesis generating and recognize the importance of performing better designed studies to answer these questions. While the data from the ACG survey are interesting, these data alone are insufficient to prove that use of OTC NSAIDs increases the risk of GI bleeding.

#### Literature cited

1. Peura DA, Lanza FL, Gostout CJ, Foutch PG. The American College of Gastroenterology Bleeding Registry: preliminary findings. *American Journal of Gastroenterology*. 1997;92:924-8
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3. Kaufman DW, Kelly JP, Rosenberg L, Anderson TE, Mitchell AA. Recent patterns of medication use in the ambulatory adult population of the United States: the Slone survey. *Jama*. 2002;287:337-44.
4. Laine L, Peterson WL. Bleeding peptic ulcer. *New England Journal of Medicine* 1994;331:717-27.

**Over the Counter Nonsteroidal Antiinflammatory Drugs  
and Risk of Gastrointestinal Bleeding. WJ Blot and JE  
Mclaughlin. Journal of Epidemiology and Biostatistics  
2000;2:137-142.**

**Critique**

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Richard C Reynolds Professor of Medicine  
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November 10, 2002

## **Summary of Methods and Results**

A case-control study was performed under the sponsorship of the American College of Gastroenterology. A survey was mailed to members of the society seeking information on patients with GI bleeding (cases) and procedure matched patients without bleeding (controls). Each gastroenterologist was asked to complete forms on up to 10 cases and controls. Cases were usually patients admitted to hospital with bleeding undergoing EGD and colonoscopy. Controls underwent the same diagnostic procedure. Information was collected on demographics, NSAID exposure within one week and dose (duration was unknown in many patients), prior history of GI bleeding, other drugs (corticosteroids, anticoagulants), habits (alcohol and tobacco). Logistic regression was used to calculate odds ratios adjusted for confounders.

There were a total of 627 cases and 590 controls. The cases were older, more frequently male, and reported more smoking and alcohol use. Cases had a prior history of GI bleeding in 29% and controls in 10%. Dyspepsia was more common in controls (58%) than cases (37%). About 75% of cases had upper GI bleeding. All models included age, gender, alcohol use, prior GI bleeding and dyspepsia symptoms. OTC ibuprofen was associated with increase risk of GI bleeding; odds ratio 2.4, 95% confidence interval, 1.5-3.9. Prescription dose NSAIDs had a comparable risk to OTC use; odds ratio 2.1, 95% confidence interval, 1.2-3.4. The association was present for both upper and lower GI bleeding although data was not presented. Risk of bleeding associated with OTC ibuprofen was 1.8 (0.8-4.1) for up to 600 mg, 2.4 (1.2-10.7) for 601-1200 mg, and 3.9 (1.2-12.9) for > 1200 mg. No statistics were provided for dose

response. The use of H-2 blockers, PPI were not controlled for in models since were relatively low frequency or were not significant confounders (data was not shown).

### ***Critique***

Overall this is a weak study that was published in a journal that is infrequently read by the medical community. The only real strength of the study is that cases are well defined. All patients underwent endoscopy to document cause of disease. However, there are many weaknesses of this study that undermine the conclusions.

1. Conceptual Framework of Question. The underlying premise of this study is that OTC use of aspirin and ibuprofen may be associated with GI bleeding. There is a substantial body of data that confirms aspirin leads to GI bleeding. However, the question related to ibuprofen is not whether OTC ibuprofen causes GI bleeding but if low dose ibuprofen leads to GI bleeding. OTC ibuprofen is often prescribed by physicians at doses equivalent to prescription doses. Thus, the question is not OTC versus prescription use of ibuprofen, but rather the dose and duration that the drug is used.

2. Case definition. While the diagnosis of the cases are defined by endoscopy, combining upper and lower GI bleeding into the case definition is inadvisable. The pathophysiology and extensive prior data strongly suggests the risk of GI bleeding is predominately limited to upper GI tract. The authors indicate that both upper and lower GI bleeding was associated with OTC ibuprofen although no data is presented for review and confirmation of this statement. Furthermore, the fact that lower GI bleeding was found to be associated with OTC ibuprofen raises significant concern of bias.

3. Selection of Controls. The controls used for this study are inappropriate and almost certainly led to important bias. The proper control group would be a random

sample of patients from the same community that cases were chosen. Hospitalized controls result in subjects that are much sicker than a typical community control. Hospitalized controls that underwent endoscopy result in controls who are both actively ill and sick enough to require an invasive procedure. While it is always difficult to know how the choice of a control influences drug exposure, it seems very likely that in this case it would lower exposure to NSAIDs. Patients with GI symptoms sick enough to require endoscopy will frequently be advised to avoid NSAIDs. Furthermore, the control group had many more patients with dyspepsia. A gastroenterologist will almost always recommend discontinuation of NSAID. Thus, the choice of this control group alone may explain the findings.

4. Validity of the Data. The methods used to collect data provided no opportunity to validate the quality of the data. Obtaining accurate drug exposure can be very difficult in a research setting where forms and procedures are used to maximize accurate recall. It is likely that accuracy of drug exposure is reduced given information was obtained as part of routine clinical practice. This is especially true when considering OTC analgesics.

5. Choice of cases and controls. Cases and controls should have been chosen randomly from eligible subjects without knowledge of the hypothesis being tested. It is not stated in the paper if the investigators were blinded to the hypothesis at the time the forms were completed and patients identified for the study. A random selection process of subjects was not used. Furthermore, patients with prior GI bleeding should have been excluded since this clearly will impact analgesic use and controlling for this variable in the analysis is unlikely to adequately control for this confounder.

6. Other Issues: The analysis never should have controlled for dyspepsia since this may be controlling for precursor of the cause of bleeding in many patients; peptic ulcer disease. No statistical testing was reported for the dose response relationship. Duration of exposure has been shown in many studies to be related to GI bleeding but this information was not accurately captured in this study. The studies that are included in Table 5 included patients who were not taking OTC NSAIDs.