

**Citizen Petition  
Summary**

## Citizen Petition Summary

### 1.0 Contents of this Citizen Petition

Presented in this Petition are the final study reports for the three new clinical trials and an integrated summary of the evidence supporting caffeine adjuvancy with APAP. This summary concludes that caffeine adjuvancy with APAP has been demonstrated in a variety of pain models and study designs as evidenced by statistically significant increases in pain relief and decreases in pain intensity compared to APAP alone. In addition, this petition includes new data and analyses, as well as a comprehensive assessment of worldwide caffeine safety data that supports the Category I status of the 130mg dose in combination with aspirin (ASA) and APAP or with APAP alone. To further address questions from the Agency's April 13, 2001 letter, the safety assessment includes a review of postmarketing surveillance data that includes both single and multiple dose use, as well as a summary of the worldwide literature related to animal and human studies investigating potential acetaminophen/caffeine interactions.

### 2.0 Background

Bristol-Myers Squibb (BMS) markets the Excedrin<sup>®</sup> line of over-the-counter (OTC) internal analgesic drug products, including Excedrin<sup>®</sup> Extra Strength (ASA 500mg/APAP 500mg/caffeine 130mg per dose) and Aspirin Free Excedrin<sup>®</sup> (APAP 1000mg/caffeine 130mg per dose), which are regulated under the Proposed Rule for Internal Analgesic, Antipyretic and Antirheumatic Drug Products for OTC Human Use. The current labeled indications for these products are "for the temporary relief of minor aches and pains associated with headache, sinusitis, a cold, muscular aches, premenstrual and menstrual cramps, toothache, and for the minor pain from arthritis." The current formulation of Excedrin<sup>®</sup> Extra Strength has been marketed in the US since 1978, and Aspirin Free Excedrin<sup>®</sup> has been marketed in the US since 1990. BMS also markets Excedrin<sup>®</sup> Migraine (ASA 500mg/APAP 500mg/caffeine 130mg per dose), which is regulated under NDA 20-802. The current indication is for the OTC treatment of migraine. This product was first approved in 1998. Since 1978, over 47 billion tablets of Excedrin<sup>®</sup> Extra Strength, Aspirin Free Excedrin<sup>®</sup> and Excedrin<sup>®</sup> Migraine have been distributed.

The safety and efficacy of caffeine as an analgesic adjuvant was initially reviewed by FDA's Advisory Review Panel for OTC Internal Analgesic, Antipyretic and Antirheumatic Drug Products (Panel) during the period 1972 through 1977. Although the Panel stated that the inclusion of caffeine theoretically "could be a factor in analgesic abuse," it concluded that (a) there was "insufficient evidence" to justify a warning regarding caffeine, and (b) the "potential benefits outweigh this risk" (42 FR 35484-85). The Panel thus placed

caffeine in Category I for safety. With respect to effectiveness, the Panel found there was evidence to suggest that caffeine-containing analgesics were more effective than non-caffeinated analgesics alone (42 FR 35483). Because the data available at that time were considered limited, however, the Panel concluded that additional clinical studies needed to be performed in order to conclusively determine that caffeine was an effective analgesic adjuvant when used in combination with ASA and APAP, or APAP alone (42 FR 35482). Accordingly, the Panel placed caffeine in Category III for effectiveness with the expectation that it could attain Category I status if one or more adequate and well-controlled studies were performed demonstrating that caffeine provides a statistically significant contribution to the overall effectiveness of the analgesic product (42 FR 35483, 35489)].

Subsequently, BMS engaged in a continuing dialogue with the Agency in an effort to address the Panel's and FDA's concerns regarding the efficacy of caffeine as an analgesic adjuvant. As part of that dialogue, BMS conducted new trials and submitted significant new data and information in filings dating from 1973 through 1988. The submissions included adequate and well-controlled studies involving different designs (bioassay, parallel head-to-head, crossover head-to-head), different pain models (tension headache, dental, postpartum), and different analgesic bases (ASA/APAP combinations and APAP alone). These filings included a 1982 Citizen Petition to reopen the administrative record to include new clinical studies designed to address the Agency's concerns. While the Petition was denied in 1983, the Agency requested and received further detail on several of the studies submitted in the Citizen Petition. The following year, Laska et al. provided a meta-analysis of the results of studies conducted by BMS in over 10,000 subjects, comparing the potency of various analgesic bases combined with caffeine, relative to an analgesic alone. A series of meetings, discussions and submissions followed over the next few years.

In November 1988, FDA published the Proposed Rule for Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for OTC Human Use (53 FR 46204) and concluded that additional data were needed to classify caffeine as Category I as an analgesic adjuvant. Based upon comments related to the caffeine dose, FDA agreed to change "the Panel's recommended single dose of 65mg caffeine to 75mg caffeine as an analgesic adjuvant, not to exceed a single adult dose of 150mg or a maximum daily dose of 600mg" (53 FR 46251). In making this change, the Agency noted that a 150mg single adult dose was well within the 100-200mg dose range for caffeine recommended by the Sleep-Aid Panel for stimulant drug products (53 FR 46244).

In response to the 1988 Proposed Rule, BMS submitted data from six additional clinical trials which demonstrated that the combination of ASA 500mg/APAP 500mg/caffeine 130mg provided superior efficacy to APAP 1000mg alone, and that this difference was statistically and clinically significant. The following year, BMS submitted the results from three new clinical trials (two crossover headache

studies and one dental pain study) comparing the efficacy of the combination of APAP 1000mg/caffeine 130mg with APAP 1000mg alone. The headache studies demonstrated that the combination of APAP 1000mg/caffeine 130mg provided superior efficacy to APAP 1000mg alone. Although the results of the parallel design dental study did not achieve statistical significance, the differences between APAP 1000mg/caffeine 130mg and APAP 1000mg alone were supportive of caffeine adjuvancy.

The Office of OTC Drug Evaluation (Office) concluded, in an April 1995 Feedback Letter to Industry, that while caffeine was an effective analgesic adjuvant when combined with ASA or the ASA/APAP combination, the evidence was insufficient to conclude the analgesic adjuvancy of caffeine when combined with APAP alone. The Office based the decision relative to APAP/caffeine on the conclusion that the statistically significant differences between the caffeinated and non-caffeinated analgesics observed in the crossover design headache clinical trials could be due to a potential carryover effect. Moreover, the Office, in its April 1995 Feedback Letter, advised BMS that it would recommend to the Commissioner that the single dose of caffeine for use as an analgesic adjuvant be limited to 64/65mg. This recommendation was based upon the Office's conclusion that "it is prudent to limit the amount of caffeine contained in OTC analgesic drug products until such time as more definitive data on caffeine's potential to foster analgesic misuse are available." In order to reduce this potential risk, the Office concluded, "the final monograph will limit the maximum amount of caffeine permitted in analgesic combinations to the minimum effective caffeine dose demonstrated by the data." In August 1995, BMS submitted a response to the Office's Feedback Letter setting forth the scientific basis in support of the Category I status of caffeine 130mg as an analgesic adjuvant in combination with APAP alone, as well as information confirming the safety of the 130mg formulation.

In 1997, FDA again reviewed caffeine 130mg safety as part of its review of NDA 20-802 for Excedrin<sup>®</sup> Migraine. In July 1997, a joint meeting of the FDA Advisory Committees reviewed the safety and efficacy of Excedrin<sup>®</sup> for the treatment of migraine headache pain and recommended approval of the NDA. The Agency approved the NDA in January 1998 with a dosing regimen of 2 tablets (ASA 500mg, APAP 500mg, caffeine 130mg) every 6 hours, not to exceed 8 tablets in 24 hours. On October 7, 1999, following another FDA review, Supplement No. 002 to NDA 20-802 was approved to expand the indication to treat the entire migraine complex, with a dosing regimen in line with prescription migraine treatments, *i.e.*, 2 tablets in a 24-hour period.

Since that time, BMS has conducted three new, parallel, double-blind, randomized clinical trials designed to conclusively establish caffeine adjuvancy with APAP. One study was conducted in a tension headache model and two in a dental model. The new tension headache trial was conducted as a parallel group study designed to confirm the results of the earlier crossover studies, thereby

addressing the Agency's concern about potential carryover effect. The two new parallel group dental studies were conducted to supplement the earlier dental study.

### **3.0 Analgesic Adjuvancy of Caffeine with Acetaminophen**

#### **3.1 Scope of the Report**

The report entitled "The Analgesic Adjuvancy of Caffeine in Combination with Acetaminophen" includes data from three new, parallel, double-blind, randomized, placebo-controlled trials that demonstrate caffeine adjuvancy with APAP. One trial was conducted in the tension headache model (HPD-H203) and two trials were conducted in the dental pain model (HPD-D104 and HPD-D105). The new tension headache trial (HPD-H203) was conducted to confirm results of the earlier crossover design headache trials.

Data from these three new trials confirm the positive caffeine adjuvancy findings of previously submitted studies in headache, dental, and postpartum bioassay pain models.

Overall, BMS has completed a total of 17 clinical studies that specifically examined the analgesic adjuvancy of caffeine in combination with APAP. Fourteen (14) of these studies have previously been submitted to FDA. The 17 studies are summarized in Table 1.0, where they are classified in two ways. First they are classified as either head-to-head direct comparison studies, or as bioassay relative potency comparison studies, based on the analytical methodology employed to evaluate response differences between treatments. The studies are further classified according to the pain model investigated: tension-type headache pain, postoperative dental pain, and postpartum pain.

Table 1.0 BMS Clinical Study Program Caffeine's Analgesic Adjuvancy With Acetaminophen							
Pain Model Study No.	Study Design Features <sup>A</sup>	Subjects N	Treatment Groups			Study Dates	Submission Dates To FDA Initial (Follow-Up)
			No. <sup>B</sup>	APAP mg	APAP mg +CAF mg		
<b>Head-to-Head Direct Comparison Studies</b>							
<b>Tension-Type Headache Pain</b>							
HPD-H203	DB, PG, R, PC	1104	3	1000	1000 +130	10/97-5/98	NEW
170-01-88	DB, CO, R, PC	441	3	1000	1000 +130	2/88-1/89	11/16/89 (5/93, 5/95)
170-02-88	DB, CO, R, PC	442	3	1000	1000 +130	2/88-10/88	11/16/89 (5/93, 5/95)
<b>Postoperative Dental Pain</b>							
HPD-D104	DB, PG, R, PC	1009	3	1000	1000 +130	3/97-12/97	NEW
HPD-D105	DB, PG, R, PC	1015	3	1000	1000 +65	4/97-12/97	NEW
171-01-88	DB, PG, R, PC	534	3	1000	1000 +130	1/88-9/88	11/16/89 (5/93)
<b>Bioassay Relative Potency Comparison Studies</b>							
<b>Postpartum Pain</b>							
2255	DB, PG, R, PC	739	7	500, 1000, 2000	500, 1000, 2000 +65,+130,+260	77-79	9/27/82 (11/83, 2/85, 11/89, 5/93, 5/95)
2576	DB, PG, R, PC	699	7	500, 1000, 1500	500, 1000, 1500 +65,+130,+195	7/79-6/81	9/27/82 (11/83, 2/85, 11/89, 5/93)
2577	DB, PG, R, PC	227	7	500, 1000, 1500	500, 1000, 1500 +65,+130,+195	9/79-9/81	9/27/82 (11/83, 2/85, 11/89, 5/93)
2578	DB, PG, R, PC	373	7	500, 1000, 1500	500, 1000, 1500 +65,+130,+195	11/79-2/82	9/27/82 (11/83, 2/85, 11/89, 5/93)
2579	DB, PG, R, PC	434	7	500, 1000, 1500	500, 1000, 1500 +65,+130,+195	1/80-3/81	9/27/82 (11/83, 2/85, 11/89, 5/93)
2580	DB, PG, R, PC	538	7	500, 1000, 1500	500, 1000, 1500 +65,+130,+195	4/80-4/81	9/27/82 (11/83, 2/85, 11/89, 5/93)
2581	DB, PG, R, PC	414	7	500, 1000, 1500	500, 1000, 1500 +65,+130,+195	1985	10/30/1986
<b>Postoperative Dental Pain</b>							
2569	DB, PG, R	173	4	1000,1500	1000,1500 +130,+195	10/80- 10/81	9/27/82 (11/89, 5/93)
2711	DB, CO, R, PC	48	5	500	0,500 +65, 65		9/27/82 (11/83, 2/85)
2570	DB, PG, R, PC	196	7	500, 1000, 2000	500, 1000, 2000 +65,+130,+260	2/80-9/81	10/30/86 (11/89, 5/93)
2571	DB, PG, R, PC	386	7	500, 1000, 2000	500, 1000, 2000 +65,+130,+260	3/80-1/83	10/30/86 (11/89, 5/93)

<sup>A</sup> DB = Double-Blind; PG = Parallel-Groups; CO = Crossover; R = Randomized; PC = Placebo-Controlled

<sup>B</sup> Number of treatment groups includes Placebo treatment group for each study, except Postoperative Dental Pain Study No. 2569, which was not placebo-controlled

### 3.2 Focus of the Report

This document provides two levels of evidence supporting the adjuvancy of caffeine when combined with APAP. Primary support consists of six head-to-head trials. Three of these trials are the new trials HPD-H203, HPD-D104, and HPD-D105. The other three trials (170-01-88, 170-02-88, and 171-01-88) were submitted to the FDA in 1989.

Secondary support includes data from 11 bioassay studies that were submitted to the agency in 1982 and 1986.

### **Primary Support – Head-to-Head Trials**

HPD-H203 (tension-type headache) HPD-D104 (dental pain) and HPD-D105 (dental pain) are new head-to-head studies, as mentioned above, while Studies 170-01-88, 170-02-88 (tension-type headache) and 171-01-88 (dental pain) are previously submitted APAP/CAF vs. APAP head-to-head studies. These six studies, considered individually, provide substantial evidence of the analgesic adjuvant effect of caffeine given in combination with APAP, and when pooled, allow an accurate estimate of the magnitude of caffeine's adjuvant effect. This estimate is consistent with the prior published estimate.

These six head-to-head comparisons of APAP/CAF with APAP alone were adequately designed and powered to show both the analgesic adjuvant effect of caffeine and superiority of the active treatments over placebo in the different pain models. Considered together, they constitute substantial evidence of the analgesic adjuvancy of caffeine in combination with APAP and support Category I status in the Internal Analgesic Monograph.

### **Secondary Support - Bioassay Trials**

In addition to the six head-to-head studies mentioned above, BMS has completed a total of 11 double-blind, randomized, placebo-controlled, parallel groups, relative potency single-dose bioassays comparing multiples of APAP/CAF in a fixed 500 mg/65 mg ratio with corresponding multiples of APAP alone. Four of these studies were conducted in a dental pain model (Studies 2711 and 2569-2571), while the other seven were conducted in a postpartum pain model (Studies 2255 and 2576-2581).

FDA concluded that in the aggregate, these bioassay trials do not constitute substantial evidence that caffeine potentiates the analgesic effect of APAP. The Agency's criticism was that intra-study APAP/CAF vs. APAP pairwise comparisons by APAP dose did not show consistent superiority for the combination. However, it should be noted that the studies were neither designed nor powered to sustain such analyses.

The BMS dental pain relative potency studies showed weak and inconsistent evidence of an analgesic adjuvant effect of caffeine combined with APAP, probably as a result of lesser sensitivity of the dental pain model. To the extent that these studies are supportive of the analgesic adjuvancy of caffeine combined with APAP, they will be discussed briefly, but are not the primary focus of the efficacy report.

The postpartum studies, on the other hand, provide strong evidence of caffeine's analgesic adjuvancy effect for APAP, and these studies will be considered in greater detail.

### **3.3 Discussion/Summary and Conclusions of the Report**

#### **3.3.1 Discussion/Summary of the Report**

During the past three decades, BMS has submitted considerable evidence in support of caffeine adjuvancy. In 1995, the FDA issued a Feedback Letter to Industry, which concluded that while caffeine was an adjuvant when combined with ASA alone or with the combination of ASA/APAP, there was insufficient evidence to demonstrate that caffeine was an adjuvant when combined with APAP alone. FDA based this decision on concern about potential differential carryover effects in the crossover tension headache trials. In August 1995, BMS responded to the April 1995 FDA Feedback Letter, affirming the position that previously submitted clinical information provided substantial evidence of caffeine adjuvancy with APAP.

Since that time BMS has conducted three new, randomized, double-blind, placebo-controlled, head-to-head clinical trials assessing the analgesic adjuvant effect of caffeine when combined with APAP. One study was conducted in a tension headache model (HPD-H203), while the other two were conducted in a dental model (HPD-D104 and HPD-D105). The new parallel design tension headache trial (HPD-H203) was conducted to confirm the results of the earlier crossover design headache trials. Results of these 3 new trials considered in conjunction with results of earlier trials in tension-type headache, dental pain and postpartum pain models constitute strong evidence for caffeine adjuvancy with APAP, and provide a firm basis for the conclusion that caffeine potentiates the analgesic effectiveness of APAP, to a clinically relevant degree.

#### **Efficacy Summary**

##### **Headache Model**

Caffeine adjuvancy with APAP was demonstrated in the new, parallel design, headache trial (HPD-H203) which confirmed the results of the earlier crossover headache trials (170-01-88, 170-02-88). Similarly, the pooled analysis of headache studies, HPD-H203 and the first treated headache of the crossover trials, 170-01-88 and 170-02-88, also demonstrated caffeine adjuvancy with APAP (Figure A and Figure B).

- Study HPD-H203, the new, parallel, double-blind, randomized, placebo-controlled trial demonstrated caffeine adjuvancy with APAP as evidenced by:

- APAP/CAF was statistically superior to APAP alone for PID from 75 minutes through 4 hours, and to placebo from 30 minutes through 4 hours (Figure A). APAP/CAF was superior to APAP alone and to placebo for SPID4 and MAXPID.
- APAP/CAF was statistically superior to APAP alone for PAR from 75 minutes through 4 hours, and to placebo from 45 minutes through 4 hours (Figure B). APAP/CAF was statistically superior to APAP alone and placebo for TOTPAR4 and MAXPAR.
- Studies 170-01-88 and 170-02-88, two earlier crossover, double-blind, randomized, placebo-controlled trials each demonstrated caffeine adjuvancy with APAP as evidenced by:
  - 170-01-88
    - APAP/CAF was statistically superior to APAP alone and placebo for PID from 30 minutes through 4 hours (Figure A), MAXPID, SPID1, and SPID4.
    - APAP/CAF was statistically superior to APAP alone and to placebo for PAR from 30 minutes through 4 hours (Figure B), MAXPAR, TOTPAR1 and TOTPAR4.
  - 170-02-88
    - APAP/CAF was statistically superior to APAP alone and placebo for PID from 30 minutes through 4 hours (Figure A), MAXPID, SPID1, and SPID4.
    - APAP/CAF was statistically superior to APAP alone and to placebo for PAR from 30 minutes through 4 hours (Figure B), MAXPAR, TOTPAR1 and TOTPAR4.
- Pooled analysis of headache studies (HPD-H203; and first treated headache of the cross-over trials, 170-01-88 and 170-02-88) demonstrated caffeine adjuvancy with APAP as evidenced by:
  - APAP/CAF statistically superior to APAP alone for PID from 60 minutes through 4 hours (Figure A) and to placebo from 30 minutes through 4 hours. APAP/CAF was statistically superior to APAP alone and to placebo for MAXPID, SPID1 and SPID4.
  - APAP/CAF statistically superior to APAP alone and to placebo for PAR at 30 minutes and from 60 minutes through 4 hours (Figure B), MAXPAR, TOTPAR1, and TOTPAR4.

#### Dental Pain Model

Caffeine adjuvancy with APAP was demonstrated in two new dental studies (HPD-D105, HPD-D104).

In Study HPD-D104, statistical significance in favor of APAP/CAF over APAP alone was achieved at fewer timepoints than in Study D105. In an earlier dental study (171-01-88), while both APAP/CAF and APAP alone were significantly superior to placebo, the combination APAP/CAF was not significantly better than APAP alone due, in part, to the small sample size. However, the treatment effect observed in Study 171-01-88 was in favor of APAP/CAF over APAP and was similar in magnitude to that seen in HPD-D104 and HPD-D105. Similarly, the pooled analysis of dental trials, HPD-D104, HPD-D105, 171-01-88, demonstrated caffeine adjuvancy with APAP (Figure C and Figure D).

- Study HPD-D105 (APAP 1000mg/CAF 65mg) a new parallel, randomized, double-blind, placebo-controlled trial demonstrated caffeine adjuvancy with APAP as evidenced by:
  - APAP/CAF was statistically superior to APAP alone for PID from 45 minutes through 4 hours, and to placebo from 15 minutes through 4 hours (Figure C). APAP/CAF was also statistically superior to APAP alone and placebo for MAXPID, SPID1, AND SPID4.
  - APAP/CAF was statistically superior to APAP alone for PAR from 45 minutes through 4 hours, and to placebo from 15 minutes through 4 hours (Figure D). APAP/CAF was statistically superior to APAP alone and to placebo for MAXPAR, TOTPAR1, and TOTPAR4.
- Study HPD-D104 (APAP 1000mg/CAF 130mg) a new parallel, randomized, double-blind, placebo-controlled trial demonstrated caffeine adjuvancy with APAP as evidenced by:
  - APAP/CAF was statistically superior to APAP alone for PID at 30 minutes, and to placebo from 15 minutes through 4 hours (Figure C).
  - APAP/CAF was statistically superior to APAP alone for PAR at 15, 30, 60 and 75 minutes, and to placebo from 15 minutes through 4 hours (Figure D). APAP/CAF was statistically superior to APAP for TOTPAR1, and to placebo for MAXPAR, TOTPAR1, and TOTPAR4.
- In Study 171-01-88 (APAP 1000mg/CAF 130mg), an earlier parallel, randomized, double-blind, placebo-controlled trial, although statistically significant differences from APAP alone were not demonstrated due to the small sample size; treatment effects, however, were in the range of those seen in HPD-D104 and HPD-D105, and favored APAP/CAF over APAP alone (Figure C and Figure D).
- Pooled analysis of all dental studies, HPD-D104, HPD-D105, and 171-01-88, demonstrated caffeine adjuvancy as evidenced by:
  - APAP/CAF statistically superior to APAP alone for PID from 30 minutes through 3 hours, and to placebo from 15 minutes through 4 hours (Figure C). APAP/CAF was also statistically superior to APAP alone and to placebo for MAXPID, SPID1, and SPID4.

- APAP/CAF was statistically superior to APAP alone for PAR from 15 min through 3 hours (Figure D), and to placebo from 15 minutes through 4 hours. APAP/CAF was also statistically superior to APAP alone and to placebo for MAXPAR, TOTPAR1, and TOTPAR4.

### Postpartum Pain Model

Caffeine adjuvancy was demonstrated in the pooled postpartum/bioassay trials.

- Studies 2255, 2576, 2577, 2578, 2579, 2580 demonstrated caffeine adjuvancy with APAP as evidenced by:
  - APAP/CAF statistically superior to APAP with relative potency estimates of 1.28 for SPID4 and 1.31 for TOTPAR4, indicating approximately 1300mg APAP would be required to provide comparable relief to APAP 1000mg/CAF 130mg.

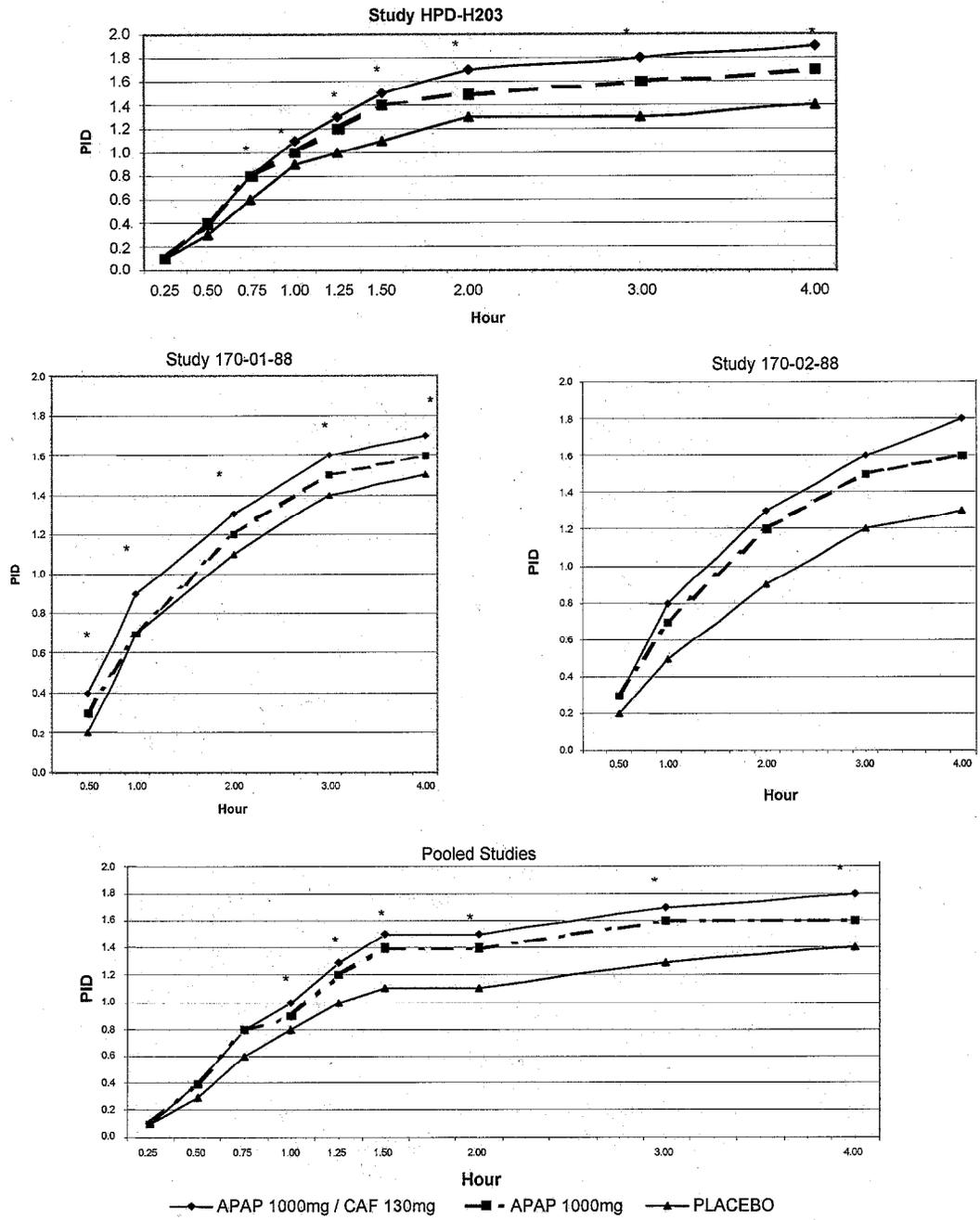
### Safety Summary

Although incidence rates for both gastrointestinal and nervous system were slightly higher for APAP/CAF than for APAP alone in the head-to-head studies, none of the adverse events in either of the categories was of a serious nature. Overall, the APAP/CAF combination was well tolerated by the subjects in these trials. Adverse events were consistent with the safety profile of the individual components. Since 1990, the APAP 1000 mg/CAF 130mg combination has been marketed in the US by BMS as Aspirin Free Excedrin<sup>®</sup>. Since that time, more than 2.5 billion tablets have been sold. The safety event profile is well characterized.

### **3.3.2 Conclusions of the Report**

- Caffeine adjuvancy with APAP has been demonstrated in a variety of pain models (headache, dental, postpartum) and study designs (parallel, cross-over, bioassay) as evidenced by statistically significant increases in pain relief and decreases in pain intensity compared to APAP alone.
- Caffeine adjuvancy with APAP allows consumers to obtain better pain relief than could be expected with the analgesic base alone.
- Caffeine adjuvancy with APAP, currently the most commonly used analgesic in the US, provides a meaningful benefit to consumers.
- The combination of APAP with caffeine is safe and well tolerated with demonstrated caffeine adjuvancy.

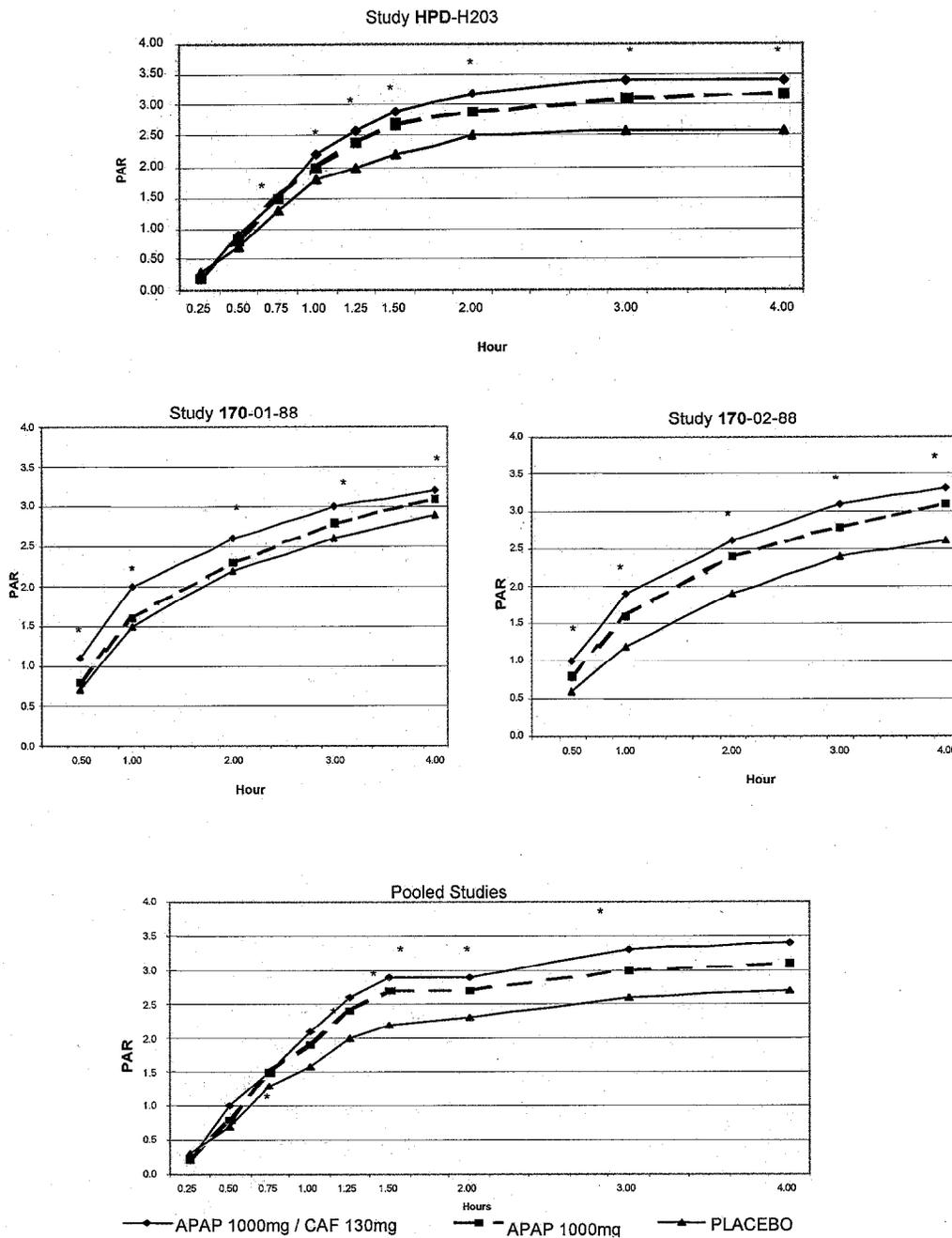
**Figure A**  
**Pain Intensity Difference**  
**Tension Headache (ITT)**



\* APAP 1000 mg/CAF 130 mg significantly greater than APAP 1000 mg

**BRISTOL-MYERS SQUIBB**  
 Hillside, New Jersey 07205

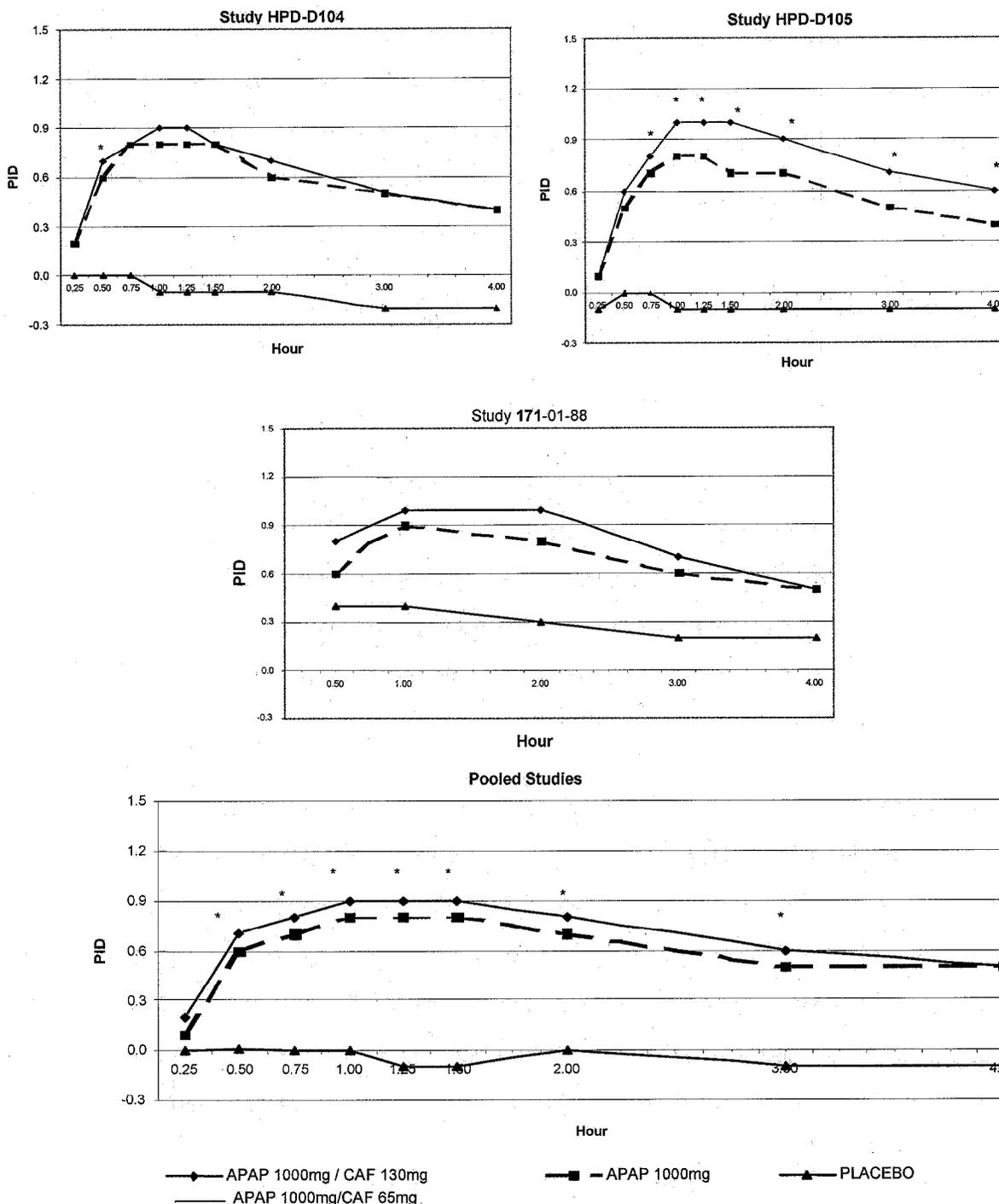
### Figure B Pain Relief Tension Headache (ITT)



\* APAP 1000 mg/CAF 130 mg significantly greater than APAP 1000 mg

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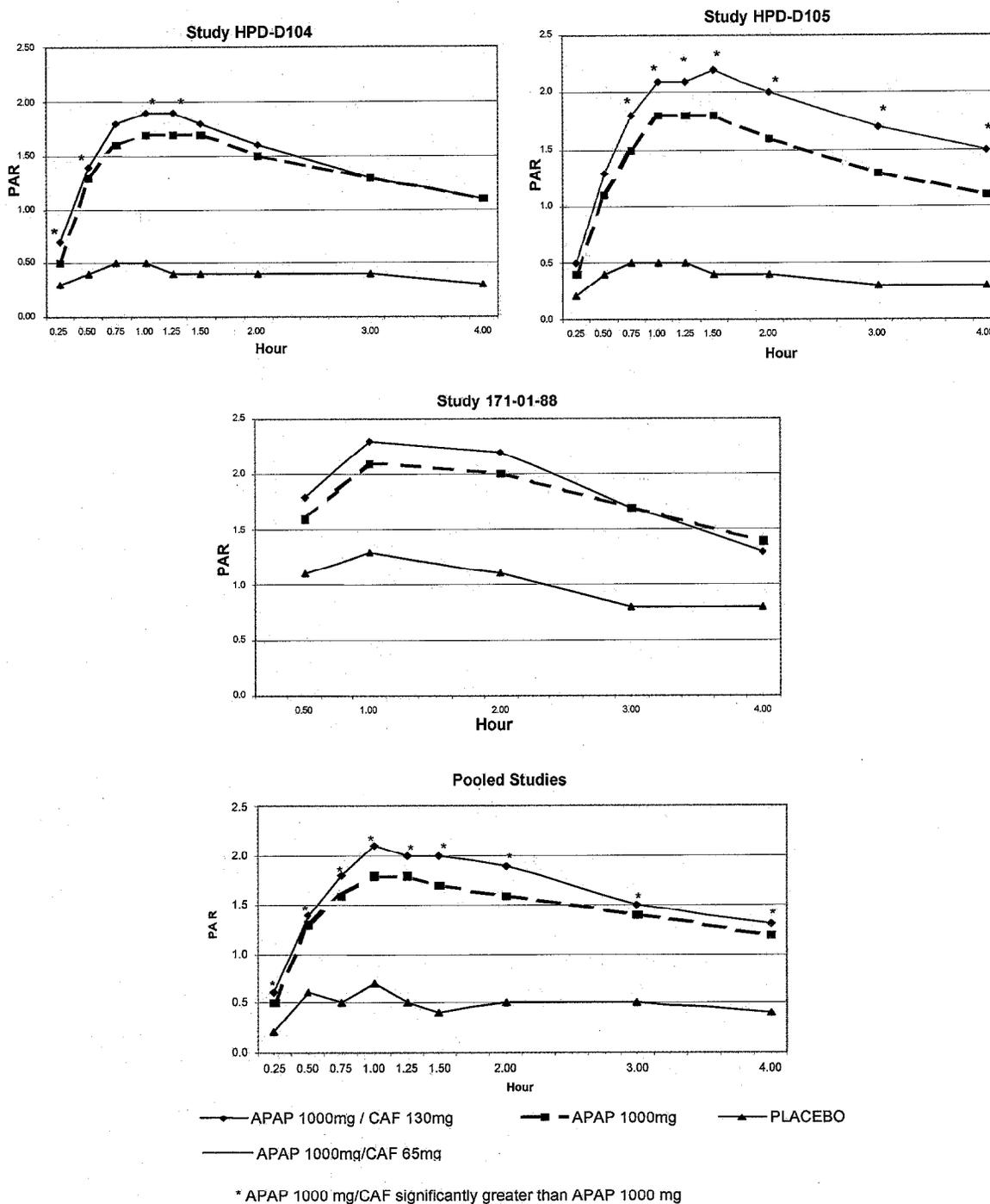
Figure C  
Pain Intensity Difference  
Dental Pain (ITT)



\* APAP 1000 mg/CAF significantly greater than APAP 1000 mg

**BRISTOL-MYERS SQUIBB**  
Hillside, New Jersey 07205

Figure D  
Pain Relief  
Dental Pain (ITT)



BRISTOL-MYERS SQUIBB  
Hillside, New Jersey 07205

## 4.0 Safety

### 4.1 Scope of the Safety Report

In order to address the 1995 FDA position that "it is prudent to limit the amount of caffeine contained in OTC analgesic drug products until such time as more definitive data on caffeine's potential to foster analgesic misuse are available," the report entitled, "Safety Assessment Supporting Caffeine 130mg When Combined with Acetaminophen or Aspirin/Acetaminophen" assesses the safety of 130mg caffeine when used as an analgesic adjuvant in Excedrin® products. To further address concerns from the Agency's April 13, 2001 letter, the safety assessment includes a review of postmarketing surveillance data that includes both single and multiple dose use, as well as a summary of the worldwide literature related to animal and human studies investigating potential acetaminophen/caffeine interactions.

The safety report establishes that:

- The addition of caffeine to oral analgesic products does not negatively impact the safety profile of individual or combination analgesics, such that unique or enhanced toxicities are produced.
- There is no evidence that there is a difference in the safety profile between analgesics co-formulated with caffeine 130mg versus 65mg.
- In consumer use surveys, the usage pattern of caffeinated analgesic products is no different from that of non-caffeinated analgesics.
- Caffeine does not foster analgesic misuse.

### 4.2 Background to the Safety Report

Caffeine is regularly consumed by more than 80% of the US population with daily consumption of 170-300mg (2.4-4.0 mg/kg) per adult, mostly as coffee and caffeinated soft drinks. Medicinal sources of caffeine account for less than 5% of caffeine use and consist primarily of single ingredient caffeine and caffeine co-formulated with other therapeutically active ingredients. The caffeine content ranges from 100-200mg per dose in CNS stimulant products and from 32-130mg per dose in caffeinated analgesic products. For perspective, 100mg caffeine is roughly equivalent to the amount contained in a cup of coffee.

Caffeine is a well documented analgesic adjuvant. The results of numerous trials indicate that approximately 40% more analgesic base would be required to provide pain relief equivalent to that of the caffeinated analgesic. Therefore, the addition of caffeine to analgesics allows consumers to receive greater pain relief than could be expected with the analgesic base alone. In addition, given the known safety concerns associated with excessive analgesic use, the "analgesic sparing" effect of caffeine may actually offer significant therapeutic benefit. Furthermore, APAP 500mg/ASA 500mg/CAF 130mg has been demonstrated to

be more efficacious than APAP 1000mg in multiple analgesic models and has also been shown to be more efficacious than ibuprofen 400mg in the treatment of acute migraine headache.

#### 4.3 Methods used in the Safety Report

The Degge Group, Ltd. conducted the data assessment. Sources of data, which were reviewed for this assessment, include:

- Published literature including clinical trials, individual case reports, epidemiological studies
- Bristol-Myers Squibb (BMS)-sponsored clinical trials data on Excedrin<sup>®</sup> Extra Strength, Excedrin<sup>®</sup> Migraine, and Aspirin Free Excedrin<sup>®</sup>
- BMS data from the Excedrin<sup>®</sup> Migraine NDA and sNDA
- FDA documents relating to OTC Monographs on Internal Analgesic Products and Stimulant Products
- Worldwide spontaneous adverse event data (internal BMS; World Health Organization; FDA Spontaneous Adverse Event Databases)
- Data obtained through the American Association of Poison Control Centers, Toxic Exposure Surveillance System (TESS),
- Data from the Drug Abuse Warning Network (DAWN)
- Drug distribution data (BMS data on file)
- Consumer usage data (The Gallup Organization)

#### 4.4 Human Exposure Data for Excedrin<sup>®</sup> Products

Excedrin<sup>®</sup> products are sold worldwide with the majority of sales in the US. Excedrin<sup>®</sup> Extra Strength has been marketed in the US in its current formulation since 1978 and Aspirin Free Excedrin<sup>®</sup> since 1990. Excedrin<sup>®</sup> Migraine, which is the identical formulation as Excedrin<sup>®</sup> Extra Strength, was approved under NDA 20-802 and launched in 1998. US Sales estimates for each product are as follows:

	Excedrin <sup>®</sup> Extra Strength 1978-Apr 2001	Excedrin <sup>®</sup> Migraine 1998-April 2001	Aspirin Free Excedrin <sup>®</sup> 1990-Apr 2001	Total
Total Tablets Sold (billions)	41.2	2.9	2.9	47

Since OTC products such as Excedrin<sup>®</sup> are often used by more than one family member, it is difficult to estimate consumer exposure from sales data. However, considering the extensive exposure based on sales combined with consumer use

patterns, it is reasonable to suggest that hundreds of millions of consumers worldwide have been exposed to Excedrin<sup>®</sup> since market introduction.

#### **4.5 Safety Assessment of Caffeine as a Single Ingredient**

The most notable effects of caffeine are its behavioral effects, which are exhibited with considerable inter-subject variability. At low to moderate doses, these effects are often perceived as positive (e.g. increased mental alertness, increased energy, increased ability to concentrate). As the dose of caffeine increases above 200mg, caffeine can induce undesirable effects (e.g. headache, anxiety, nervousness, irritability, GI disturbances). This pattern of effects, described as an "inverted-U-shape," leads most consumers to adjust their intake of caffeine in order to minimize the undesirable effects.

The long-term health consequences of caffeine have been extensively debated. Most of the epidemiologic research on these issues has found a weak to no association with caffeine, especially in amounts of less than 5 cups coffee per day. Furthermore, some recent data suggests that caffeine may even exert some positive health effects, such as prevention of colorectal cancer and Parkinson's Disease.

An examination of the spontaneous AEs from the BMS, FDA, and WHO AE databases for single ingredient caffeine revealed that the reported AEs were generally consistent with the pharmacologic properties of caffeine and the safety profile described in the literature.

Based on data from the BMS, FDA, WHO, and TESS databases, the majority of caffeine single ingredient overdoses resulted in mild to non-existent clinical events and full recovery, although rare deaths were reported. In the FDA database, which contained 2 reports of fatal overdose with single ingredient caffeine, the consumers had ingested other drugs concurrently with caffeine which were also considered suspect by the reporter.

These data do not signal any new or unexpected safety concerns with caffeine single ingredient products.

#### **4.6 Safety Assessment of OTC Caffeinated Analgesic Products**

The focus of this section is a brief review of the established overall safety profile of acetaminophen, aspirin and caffeinated analgesic products, followed by a discussion of available information on specific safety issues that have been identified by various authors, researchers, and health authorities to be of potential concern. These include the following:

- Analgesic nephropathy
- Aspirin GI bleeding
- Acetaminophen hepatotoxicity
- Overdose of caffeinated analgesics
- Rebound headache
- Caffeine dependence

For each topic, relevant information from the published literature, BMS-conducted clinical trials, spontaneous AE reports, TESS, and DAWN were reviewed.

#### **4.6.1 Overall Safety Profile of Single Ingredient OTC Analgesics**

Acetaminophen and aspirin are two of the most frequently used medications worldwide for relief of pain and reduction of fever. Both have a long history of safe and effective OTC use.

APAP, in situations of overdose or significantly impaired hepatic function, is associated with the development of dose-dependent hepatotoxicity. Risk factors for the development of hepatotoxicity include chronic or binge alcohol use, fasting, and concomitant use of drugs that enhance cytochrome P-450 activity. The mean single threshold dose associated with development of hepatotoxicity is approximately 15g or thirty 500mg tablets in a 60kg individual.

Gastrointestinal symptoms are among the most common adverse events associated with ASA. While most GI symptoms are mild and self-limiting, more serious events also occur. GI complications secondary to NSAIDs, including ASA, account for an estimated 16,500 deaths each year among arthritis patients. Among the various NSAIDs, ASA ranks among those with the lowest relative risk of producing GI complications. Risk factors for the development of GI complications include advanced age, history of ulcer disease, concomitant use of corticosteroids, higher doses and use of multiple NSAIDs, duration of therapy <3months, concomitant use of anticoagulants, and other serious coexisting illnesses. The risk of GI complications exists at all dose levels, though it appears to increase with increasing doses.

#### **4.6.2 Overall Safety Profile of OTC Caffeinated Analgesic Products**

OTC caffeinated analgesic products have been used widely for over 40 years. The current formulations of Excedrin® Extra Strength/Excedrin® Migraine, and Aspirin Free Excedrin® have been marketed since 1978 and 1990, respectively, and have been used safely and effectively by more than 200 million consumers in the US alone. BMS clinical trial data in 17,000 subjects and 27 studies across various pain models demonstrate their safety and tolerability in short term studies.

In the postmarketing setting, a comparison of the spontaneous AEs in the BMS, FDA, and WHO databases for these products confirms that their safety profiles are generally consistent in nature and severity with the known pharmacologic profiles of the individual ingredients. Despite the frequent lack of medical confirmation and detailed medical information, these data do not signal any new or unexpected safety issues with these products.

Human Pharmacokinetic studies and postmarketing AE data do not appear to signal a clinically significant interaction between caffeine and APAP when administered concurrently in doses typically used in caffeinated analgesics.

When examined specifically for AEs of special interest with caffeinated analgesics, *i.e.*, analgesic nephropathy, hepatotoxicity, GI bleeding, overdose, rebound headache, and caffeinated analgesic dependence, the spontaneous AEs across the various databases appear to be consistent with the published literature.

Phenacetin appears to be the only clear risk factor for the development of analgesic nephropathy. Based on spontaneous AE data, analgesic nephropathy does not appear to be a clinically significant issue with caffeinated analgesics. Hepatotoxicity with caffeinated analgesics (due to the APAP component) appears to occur rarely, and based on spontaneous AE data, is not always the sole inciting drug. GI bleeding (associated with the ASA component), while relatively uncommon, is often associated with the presence of additional risk factors for GI bleeding, *e.g.* history of ulcer disease, concomitant medications also associated with GI bleeding. In overdose settings, severe toxicity will most likely be associated with the analgesic component rather than the caffeine component due to the relative toxicities of each. Most cases of overdose are associated with minimal to no symptoms and result in complete recovery. Rare occurrences of significant toxicity are frequently associated with the ingestion of multiple drugs. Epidemiologic and consumer usage data demonstrate that rebound headache is less common than previously believed and associated with the use of all analgesic products, not specifically caffeinated analgesics. And finally, while caffeine appears to possess some of the attributes of drugs of dependence (*i.e.*, psychoactive effects, drug reinforcing effects, tolerance, physical dependence), these effects are weak, often inconsistently demonstrated in humans, and do not resemble the effects produced by typical drugs of abuse such as d-amphetamine and cocaine. Caffeine and caffeinated analgesics are used safely by the vast majority of users. Rare instances of drug seeking behavior associated with caffeine are usually associated with underlying psychological illness and are frequently associated with abuse of multiple drugs, not just caffeine or caffeinated analgesics.

It is often difficult to assess the postmarketing AE reports due to the paucity of detailed medical information and presence of multiple concomitant medications and illnesses; however, when examined in the context of the extensive use of

caffeinated analgesics for over 40 years, these events appear to occur infrequently, are often associated with additional risk factors, and only rarely are they associated with severe morbidity and mortality.

#### **4.7 Consumer Usage Patterns of OTC Caffeinated Analgesic Products**

Data obtained from various sources do not show a difference between the consumer usage of caffeinated and non-caffeinated analgesic products. According to data collected by The Gallup Organization on OTC analgesics, there was no meaningful difference between consumption of caffeinated analgesics versus non-caffeinated analgesics regardless of the consumption level or amount of caffeine in the product. Furthermore, in a study of analgesic use among migraine headache patients in the UK, there was no difference in usage between caffeinated and non-caffeinated analgesics.

#### **4.8 Discussion of the Safety Report**

This section discusses the key issues and provides the basis for the conclusion that caffeine 130mg is safe and well-tolerated as an OTC analgesic adjuvant.

**The addition of caffeine to oral analgesic products does not negatively impact the safety profile of individual or combination analgesics, such that unique or enhanced toxicities are produced.**

The market experience and research over the past 40 years confirm that caffeinated analgesic products are generally well tolerated and used safely by the vast majority of consumers. However, there are several safety issues that are of potential concern with these products, due to either the individual components or the combination of ingredients. These are discussed below.

##### **Analgesic Nephropathy**

The only clear risk factor for analgesic nephropathy identified and agreed upon by experts is previous use of phenacetin-containing analgesics. A recent panel of experts convened by the regulatory authorities of Germany, Austria, and Switzerland concluded that there is insufficient evidence to conclude that analgesics, in the absence of phenacetin, are causally associated with nephropathy. Similarly, there is no evidence that the addition of caffeine to analgesics is associated with nephropathy.

The data on renal events from the BMS, FDA, and WHO revealed no spontaneous reports suggestive of analgesic nephropathy with caffeinated analgesic products.

### Hepatotoxicity

Hepatotoxicity is a well-recognized complication of APAP overdose and is not usually associated with the use of ASA or caffeine. In examining the spontaneous reports for Excedrin,<sup>®</sup> non-BMS caffeinated analgesics, and the WHO data for caffeinated analgesics, there were only 3 reports of severe hepatic injury. Alcohol was a known concurrent drug in 2 of these cases. While the scant information available for these reports limits their meaningful assessment, given the extensive population exposure of caffeinated analgesics consumed during this time period, severe hepatotoxicity appears to be a rare occurrence with caffeinated analgesics.

### GI Bleeding

GI Bleeding is a recognized complication of ASA use and is not typically associated with the use of APAP or caffeine. Over the period reviewed, BMS, FDA, and WHO received 12, 20, and 46 reports, respectively, of GI bleeding events. It is not possible to determine if some of the WHO reports are duplicates of the BMS reports. Detailed information on dose, duration, concomitant drugs and prior history of ulcer disease is not available for many of these reports, however, in the BMS data, 9 consumers reported long term use of Excedrin<sup>®</sup> and in 4 of these consumers, a history of ulcer disease was noted. In the FDA data, 10/20 cases reported additional suspect drugs which are known to also be associated with GI bleeding. Despite the limited information available for these reports, cases across the database appear to be similar in nature and severity. Furthermore, the occurrence of GI bleeding appears to be relatively uncommon with caffeinated analgesics when considering the widespread use of these products.

### Overdose

In combination analgesic products, severe toxicity will most likely be associated with the analgesic component rather than the caffeine component, due to the relative toxicities of the individual ingredients. Therefore, the dose of caffeine, 130mg, in co-formulated analgesic products, is unlikely to be a contributing factor to serious toxicity from these products.

Based on data from the BMS, FDA, WHO, and TESS databases, the majority of caffeine single ingredient and caffeinated analgesic product overdoses were associated with mild to non-existent clinical events and resulted in full recovery, although rare deaths were reported. In the FDA database which contained 2 reports of fatal overdoses with caffeine single ingredient and 3 reports of fatal overdoses with APAP/CAF, all 5 consumers had ingested additional drugs concurrently with the caffeine containing product, which were also considered suspect drugs by the reporter. The TESS data, in which co-ingestions of additional drugs were excluded from our analysis, showed a generally similar profile across all products.

### Rebound Headache

Rebound headache is a recognized potential consequence of frequent analgesic use. Based on epidemiologic data, it is believed to be uncommon (<2% in a study of 1,883 subjects with chronic daily headache), and caffeine-containing analgesics are no more likely to be associated with rebound headache than any other type of analgesic medication. When caffeine-containing analgesics are involved, the consumption level of caffeine associated with rebound headache is greater than 15g per month. The etiology of rebound headache remains unclear, however addictive behavior does not appear to be a factor for the vast majority of analgesic users. Based on this evidence, there is no reason to believe that caffeine doses of 130mg in caffeinated analgesics would result in a greater incidence of rebound headache than caffeine doses of 65mg.

### Dependence

Habitual use of caffeine has been well demonstrated among the millions of daily consumers of coffee, however, true compulsive drug seeking behavior appears to be exceedingly rare and limited to a very small subset of individuals.

The psychoactive effects of caffeine show considerable inter-subject variation, but for most individuals, positive effects are seen at low to intermediate doses, with undesirable effects becoming more prominent as dose exceeds 200mg. Doses greater than 500mg are usually associated with caffeine intoxication. Moreover, caffeine's effect on the dopaminergic system has been shown to be different from that of drugs of abuse such as d-amphetamine and cocaine.

Caffeine has also been shown to exhibit weak drug reinforcing effects. The reinforcing effects of caffeine have been described as an inverted U-shape. Lower doses (up to 50mg) are reinforcing for a small proportion of subjects and increase in frequency as the dose rises. A plateau is reached between 50-150mg and then the reinforcing effects decrease with higher doses of caffeine, due to its aversive effects.

Tolerance has been demonstrated in animals. The data are less conclusive in humans and may reflect differences in inter-individual metabolism of caffeine.

Physical dependence, characterized by sudden caffeine withdrawal, has been observed with caffeine; however, it may not be as common as previously believed and symptoms rarely interfere with daily activities. It does not appear to be a dose related phenomenon and occurs inconsistently even within individuals. The majority of data on caffeine withdrawal refers to caffeinated beverages, so it is unclear if this phenomenon would also occur with caffeinated analgesic products. However, given the time lag of 12 to 24 hours until the occurrence of symptoms following complete deprivation and the ubiquitous nature and easy availability of caffeine in beverages, a withdrawal syndrome resulting solely from discontinuation of caffeine-containing analgesics is unlikely to develop under daily conditions.

In the spontaneous AE reports databases for caffeinated analgesic products, there were 49 reports of Drug Dependence and 2 reports of Drug Abuse, the majority originating from the BMS AE database. Most of these reports are not medically confirmed and typically describe a scenario of long term Excedrin<sup>®</sup> use and the inability to discontinue use. Many of the consumers were receiving other medications and had a history of psychiatric conditions. In the absence of detailed medical data regarding dose, duration of use, concurrent medications and illnesses, meaningful assessment of these reports is difficult.

#### Summary

In summary, while there are reported occurrences of important safety issues with caffeinated analgesic products, these appear to be relatively rare given the long and widespread usage of these products and are often associated with other risk factors. No unique toxicities or signals for enhanced toxicities were observed with caffeinated analgesics compared to the individual components.

#### There is no difference in the safety profile between analgesics co-formulated with caffeine 130mg versus 65mg.

Based on the available evidence, it is not possible to differentiate the effects of 130mg versus 65mg of caffeine. Published studies demonstrate that there is considerable inter-individual variability in response, which may in part be due to differences in metabolism of caffeine. Caffeine withdrawal syndrome, less common than previously believed, does not demonstrate a dose response relationship; therefore, the specific amount of caffeine in an analgesic product is unlikely to be a factor.

A comparison of the safety profiles of 65mg and 130mg of caffeine in the BMS Aspirin Free Excedrin<sup>®</sup> trials does not show any meaningful differences in the nature, severity, or frequency of AEs between the products, although head-to-head clinical trials of 65mg versus 130mg have not been conducted.

In the spontaneous AE databases, the majority of non-BMS reports are for Anacin<sup>®</sup>, a combination analgesic containing ASA 800mg and caffeine 64mg per dose. Given the limited information available for the FDA and WHO data and the fact that Excedrin<sup>®</sup> also contains APAP, it is difficult to do more than a gross comparison of AEs reported with analgesics containing caffeine 130mg versus 65mg across databases. However, the AEs reported for both Excedrin<sup>®</sup> and Anacin<sup>®</sup>, including those reported in overdose situations, appear to be generally similar in nature and severity and do not indicate any particular trends or patterns with one product versus the other.

**The usage of caffeinated analgesic products is no different than that of non-caffeinated analgesics.**

In the US, The Gallup Organization has been measuring oral analgesic consumption since 1984. According to the Gallup tracking study of several caffeinated and non-caffeinated OTC analgesics, the mean number of OTC analgesic tablets consumed per average 4-week period per consumer over the past 10 years (1990-2000) ranged from 17.8 – 21.9 (N=50,751). The mean tablet consumption during this period was no different for caffeinated analgesic products than for non-caffeinated analgesic products. Furthermore, there was no apparent difference in consumption between caffeinated analgesics containing 130mg caffeine (Excedrin®) and those containing 64mg caffeine (Anacin®) (see table).

**Gallup Tracking Data on Oral Analgesic Mean Tablet Consumption  
per Average 4-Week Period  
1990-2000**

	Excedrin® ES (130mg caffeine per dose)	Anacin®* (64mg caffeine per dose)	Aspirin (w/o caffeine)**	Advil® (ibuprofen)	Tylenol® Extra Strength (excl. PM) (acetaminophen)
No. consumers	3,433	1,492	14,227	10,838	20,761
Mean no. of tablets per average 4-week period	17.8	20.3	21.9	17.9	17.8

\* Anacin data was available only for 1990-1997 due to low sales volume post 1997.

\*\*Aspirin data post 1997 does not specifically exclude caffeine.

A similar usage profile was also observed for "heavy users" (>30 or >180 pills per average 4-week period) of analgesics.

In a study of analgesic usage among migraine patients in the UK, there was also no difference in usage between caffeinated and non-caffeinated analgesics.

**Caffeine does not foster analgesic misuse.**

Despite extensive caffeine research over many decades, the weight of the evidence does not support the concern that the addition of caffeine to analgesic products will foster misuse. Further, there are no published experimental studies that clearly implicate caffeine in misuse, nor does consumer use experience demonstrate a misuse problem.

Given the widespread and inexpensive availability of caffeine-containing beverages, it is unlikely that analgesic combinations would be purchased for their caffeine content by those who might be attracted to caffeine's stimulant effect. Indeed, caffeine stimulant tablets (No Doz®, Vivarin®, etc.) are readily available over-the-counter, and cases of abuse are rare. This conclusion is also supported

by caffeine's physiologic profile, which is quite different from drugs of abuse, such as d-amphetamine and cocaine.

Studies in normal subjects show that reinforcement follows an inverted U-shaped function, with reinforcement rising with increased doses until it reaches a plateau between 50-150mg. With higher doses, caffeine's aversive effects discourage misuse. This opinion was corroborated by the FDA Medical Reviewer during the review of the Excedrin<sup>®</sup> Migraine NDA.

The theoretical concern that rebound or withdrawal headache may occur with cessation of caffeinated analgesic use, encouraging additional dosing, is not supported by the evidence. We now know that caffeine has low potential for drug dependence and that dependence is less common than previously thought. We also now understand that rebound headache occurs with all analgesics.

Recognizing the breadth of new data that has emerged in recent years addressing caffeine safety, other drug regulatory bodies have sought to resolve the question of potential misuse of caffeinated analgesics. In January 2000, the drug regulatory authorities of Germany, Switzerland, and Austria convened a committee of international experts to review all the relevant published literature on caffeine and caffeinated analgesics relative to misuse potential. The committee concluded that caffeine's dependence potential is low, and it appears unlikely that withdrawal could play a causative role in stimulating or sustaining analgesic intake. In addition, it concluded that, in the absence of phenacetin, there is insufficient evidence to claim that analgesics co-formulated with caffeine stimulate or sustain overuse or lead to dependence behavior.

#### **4.9 Conclusions from the Safety Report**

Based on this review of the worldwide safety literature, adverse event databases, expert reports and consumer use data that includes both single and multiple dose use, it can be concluded that:

- The safety profiles of analgesics containing 130mg caffeine per dose (ASA 500mg/APAP 500mg/caffeine 130mg; APAP 1000mg/caffeine 130mg) are well characterized and consistent with those of the individual components.
  - No new or enhanced toxicities have been found compared to the individual components.
  - Most adverse events are of a mild and self-limiting nature.
- The potential for caffeinated analgesics to foster analgesic misuse is low.
  - Caffeine has a low potential for drug dependence.
  - Caffeine's U-shaped reinforcement pattern discourages use of high doses due to aversive effects.
  - There are no published experimental studies that clearly implicate caffeine in analgesic misuse.

- Consumer usage patterns for caffeinated analgesics are similar to those for non-caffeinated analgesics.
- The safety profile of analgesics co-formulated with caffeine at 130mg and 65mg appear to be similar, based on evaluation of the worldwide safety data and consumer usage patterns.
- Caffeine at a 130mg dose is a proven analgesic adjuvant, providing statistical and clinical efficacy improvements to that of the analgesic base alone.
- The Excedrin<sup>®</sup> formulations containing caffeine 130mg have a long history of safe and effective use, and should be included in the Final Monograph.
  - Since 1978, more than 47 billion Excedrin<sup>®</sup> tablets have been used by more than 200 million US consumers.

## 5.0 Conclusions of this Citizen Petition

This Citizen Petition establishes the adjuvancy of caffeine when combined with APAP. This effect has been demonstrated in a variety of pain models and study designs, as evidenced by statistically significant increases in pain relief and decreases in pain intensity compared to APAP alone. In addition, this Citizen Petition confirms the appropriateness of the 130mg dose in combination with ASA/APAP or APAP alone. The addition of caffeine to analgesic products does not negatively impact the safety profile of individual or combined analgesic bases, and there is a low potential for caffeine to foster analgesic misuse.

While there are no adequate and well-controlled clinical trials that have directly compared the analgesic adjuvancy of the 130mg dose versus 65mg of caffeine, there is a long history of clinical and consumer experience with 64mg and 130mg caffeine doses when combined with analgesic bases. Both caffeine doses appear to have similar safety profiles and do not show any meaningful differences in the nature, severity, or frequency of adverse events. Based on consumer usage data generated by The Gallup Organization, the usage patterns of analgesics containing caffeine 130mg are not different from those of analgesics containing lower doses of caffeine or no caffeine. It would, therefore, appear to be reasonable to allow the inclusion of both 64/65mg and 130mg in the Final Internal Analgesic Monograph.