



Bristol-Myers Squibb Company

Worldwide Consumer Medicines

1350 Liberty Avenue Hillside, New Jersey 07205 908.851-2400

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July 30, 2001

Dockets Management Branch (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Attention: Charles Ganley, MD, Director
Division of OTC Drug Products (HFD-560)
Food and Drug Administration

Re: Docket No. 77N-0094
Internal Analgesic, Antipyretic, and Antirheumatic
Drug Products for Over-the-Counter Use

Citizen Petition

Dear Dr. Ganley:

The Bristol-Myers Squibb Company (BMS) is submitting this Petition pursuant to 21 CFR 10.25 and 21 CFR 10.30 to request that the Commissioner of Food and Drugs amend a Proposed Rule.

Action Requested

BMS is requesting the FDA to reopen the administrative record for the Internal Analgesic/Antipyretic Drug Products rulemaking. Specifically, BMS is requesting that the Proposed Rule (November 16, 1988, 53 FR 46204) be amended to provide for Category I status of caffeine as an OTC analgesic adjuvant when combined with acetaminophen (APAP) alone. In addition, this Petition requests Category I classification of the caffeine 130mg dose when used as an analgesic adjuvant in combination with aspirin (ASA) and APAP or with APAP alone.

Statement of Grounds

This Petition includes the final clinical study reports for three new adequate and well-controlled trials, which confirm prior clinical study results, demonstrating caffeine's effectiveness as an analgesic adjuvant in combination with APAP. An

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Statement of Grounds

This Petition includes the final clinical study reports for three new adequate and well-controlled trials, which confirm prior clinical study results, demonstrating caffeine's effectiveness as an analgesic adjuvant in combination with APAP. An

integrated summary of the evidence supporting caffeine adjuvancy with APAP has also been included. 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 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.

BMS markets the Excedrin[®] line of over-the-counter (OTC) internal analgesic drug products including Excedrin[®] Extra Strength (ASA 500mg/APAP 500mg/caffeine 130mg) and Aspirin Free Excedrin[®] (APAP 1000mg/caffeine 130mg), which are regulated under the Proposed Rule for Internal Analgesics, 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[®] Extra Strength has been marketed in the US since 1978, and Aspirin Free Excedrin[®] has been marketed in the US since 1990. BMS also markets Excedrin[®] Migraine (ASA 500mg/APAP 500mg/caffeine 130mg), 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 46.8 billion tablets of Excedrin[®] Extra Strength, Aspirin Free Excedrin[®] and Excedrin[®] 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 at 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 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[®] Migraine. In July 1997, a joint meeting of the FDA Advisory Committees reviewed the safety and efficacy of Excedrin[®] 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 design 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.

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. Also included in this Petition is a comprehensive safety assessment of caffeine that supports the Category I status of the 130mg dose in combination with ASA and APAP or with APAP alone. This assessment demonstrates that the addition of caffeine to analgesic products does not

negatively impact the safety profile of individual or combined analgesic bases, and that 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 Analgesic Monograph.

To further address the Agency's request for additional information demonstrating the incremental benefit of the caffeine 130mg dose versus 65mg, BMS is proposing to conduct a placebo controlled, dose response trial comparing the clinical effects of the combinations of ASA 500mg/APAP 500mg/caffeine 130mg and ASA 500mg/APAP 500mg/caffeine 65mg with APAP 1000mg alone. A positive dose response in such a trial would provide convincing evidence for increased analgesic effect with increased caffeine dose. It is also proposed that the results from this study be extrapolated to support the combination of APAP 1000mg/caffeine 130mg. A draft protocol outline for this proposal will be submitted to the Division for review and comment under separate cover.

Environmental Impact

BMS is claiming a categorical exclusion from the requirement to prepare an environmental assessment under 21 CFR 25.31(a). The subject of this petition is currently marketed and there will be no anticipated increase in the overall use or change in the intended uses of the product.

Economic Impact

BMS does not believe that a statement of economic impact is required. The information will be provided only when requested by the Commissioner, following review of this petition.

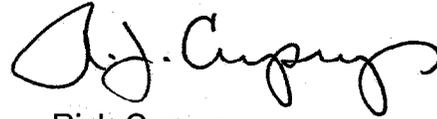
Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, that it is well grounded in fact and is warranted by existing laws and regulations, that it is not submitted for any improper purpose, such as to harass

or cause unnecessary delay, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

If you have any questions or comments regarding this petition please contact the undersigned at (908) 851-6126.

Sincerely,



Rich Cuprys
Director, Regulatory Affairs
Bristol-Myers Squibb Company
Worldwide Consumer Medicines
1350 Liberty Avenue
Hillside, NJ 07205

CC: Walt Ellenberg, Ph.D. (HFD-560)