



MEMORANDUM

Department Of Health and Human Services
Food and Drugs Administration
Center For Drug Evaluation and Research
Division of Over-the-Counter Drug Products (HFD-560)

DATE: January 15, 2002

TO: Charles Ganley, MD
Division Dir., DOTCDP, HFD-560

THROUGH: Linda M. Katz, MD, MPH *LMK*
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FROM: Rosemarie Neuner, MD, MPH *AN*
Medical Reviewer, HFD-560

RE: An Archeological Review of the Regulatory History of Over-The-Counter (OTC) Single Ingredient Acetaminophen

Documents examined in preparation of this summary:

1. The divisional file for NDA 17-053 Tylenol Extra-Strength Capsules (acetaminophen 500 mg)
2. Archival volumes 1 and 2 for NDA 17-552 Tylenol Extra-Strength Tablets (acetaminophen 500 mg)
3. Archival volumes 1.1, 2.1, 3.1, 4.1, 8.1, 12.1, 13.1, 15.1, 16.1, 17.1, and 27.1 for NDA 19-872 Tylenol Sustained-Release Caplet (acetaminophen 650 mg)
4. Proposed Rule for OTC Internal Analgesic, Antipyretic, and Antirheumatic Drug Products (21 CFR Part 343, 42 FR 35345)
5. The Tentative Final Monograph (TFM) for OTC Internal Analgesic, Antipyretic, and Antirheumatic Drug Products (53 FR 46204)

Background

Acetaminophen (APAP) is a para-aminophenol derivative that is also the active metabolite of the analgesic drug phenacetin. Although it is classified as an antipyretic analgesic agent, it can exert mild anti-inflammatory properties since it weakly inhibits prostaglandin synthesis at high doses. APAP's effectiveness as an antipyretic agent has been attributed to its effect on the hypothalamic heat-regulating center, while its analgesic efficacy is due to its ability to raise the pain threshold. In 1960, a 325 mg immediate-release tablet formulation of APAP was first approved for over-the-counter (OTC) marketing in the United States (U.S.) under the new drug approval (NDA) process for the following indications: the temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular aches, backache, for the minor pain of arthritis, for the pain of menstrual cramps and for the reduction of fever. The recommended dose of the 325 mg immediate-release APAP tablet is one to two tablets (325 to 650 mg) every 4-6 hours. The maximum daily dosage of APAP immediate-release tablets is 3,900 mg in a 24-hour period. Based on the recommendations made by the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Products, the agency classified APAP as a Category I analgesic product and included it in the Proposed Rule for OTC Internal Analgesic, Antipyretic, and Antirheumatic Products published on July 8, 1977. This document permits the marketing of adult strength, single-ingredient acetaminophen products in the U. S.

when labeled as follows: 325 mg to 650 mg every 4 hours while symptoms persist not to exceed 3,900 mg in 24 hours for not more than 10 days.

On May 15, 1975 McNeil Consumer Products, sponsor of the TYLENOL® brand of APAP, received agency approval to market a 500 mg immediate-release capsule formulation of their product called Extra Strength TYLENOL® under the new drug approval process (NDA 17-053) for the same indications as listed above. Subsequent approval of the sponsor's 500 mg immediate-release tablet formulation was granted by the agency on 1975. The recommended dose of Extra Strength TYLENOL® is two 500 mg capsules/tablets (1,000 mg) every 4-6 hours. The maximum daily dosage of Extra Strength TYLENOL® is 4,000 mg in a 24-hour period. The publication of the Tentative Final Monograph (TFM) for OTC Internal Analgesic, Antipyretic and Antirheumatic Drug Products on November 16, 1988 provided Category I classification for adult doses of immediate-release APAP products up to 1,000 mg, not to exceed 4,000 mg in 24 hours.

McNeil Consumer Products received agency approval to market a 650 mg extended-release formulation of their TYLENOL® brand of acetaminophen product called TYLENOL® Extended Relief on June 8, 1994 (NDA 19-872). The recommended dose of TYLENOL® Extended Relief is two 650 mg caplets every 8 hours swallowed whole with water. The maximum daily dosage of TYLENOL® Extended Relief is 3,900 mg in a 24-hour period. This is the only OTC acetaminophen formulation that is not marketed under the monograph process.

The following is a summary of the available efficacy and safety data that was submitted in support of regulatory decisions made by the agency regarding the 325 mg and 500 mg immediate-release formulations, and the 650 mg sustained release formulation of acetaminophen for the OTC market. (Note: Copies of agency letters to sponsors, NDA reviews, and pertinent sections of the Proposed Rule and TFM used in writing this memo can be found in the attached Appendices.)

I. 325 mg Strength, Single Ingredient, Immediate-Release APAP:

As per agency procedural policy, all NDAs for 325 mg strength, single ingredient, immediate-release APAP products were closed when this product was converted to monograph status in 1977. The specific data to support the NDA application of safety and efficacy is not available for re-review.

The Proposed Rule for OTC Internal Analgesic, Antipyretic, and Antirheumatic products published on July 8, 1977 contains an extensive discussion, by the members of the expert panel, of the data they reviewed regarding acute APAP-induced hepatotoxicity in humans. This data was generated from anecdotal reports of acute APAP poisoning in suicide patients that had been collected by the agency, the National Clearinghouse for Poison Control Centers, and case reports published in the literature. Based on the information contained in these reports, the Panel concluded that single doses of APAP less than 15 grams were not usually associated with serious hepatotoxicity in humans. This was supported by animal toxicology data that the APAP LD50 dose in rats was 770 mg/kg/day. Thus, the LD50 in man was estimated to be 400 mg/kg a day which was approximately 5 to 7 times the maximum recommended daily dose of 3,900 mg in humans who weighed between 50-70 kg. Since APAP-associated hepatotoxicity is due to glutathione depletion, the Panel deemed that the single APAP dose a less reliable measure than comparing the single toxic dose to the daily divided dose of 650 mg for estimating APAP's safety range. The Panel therefore noted in their report that the hepatotoxic dose of 15 g of APAP was 23 times the recommended single dosage of 650 mg. Thus, the Panel recommended the following warning be included as part of the labeling for APAP products: "Do not exceed recommended dosage because severe liver damage may occur." The Panel also recommended that additional studies were needed to determine if another warning was required for the use of regular doses of APAP in individuals with pre-existing liver disease.

Following the publication of the Proposed Rule which classified APAP 325 mg strength, single ingredient, immediate-release as a Category I analgesic and antipyretic product, the marketing of these products moved into the monograph system.

II. 500 mg Strength Single Ingredient Acetaminophen

On June 15, 1971, McNeil Consumer Products submitted for agency review a 505(b)(1) application for Extra Strength TYLENOL® 500 mg APAP capsule for prescription use (NDA 17-053). The sponsor's rationale for this application was that the 500 mg capsule would have greater analgesic efficacy than the than marketed 325 mg tablet formulation. In support of their submission, the sponsor included the results from 1 bioavailability study and 8 double-blind, placebo controlled, analgesic trials that evaluated the efficacy and safety of 1000 mg doses of APAP in both acute and chronic settings. A total of 229 patients with a variety of painful conditions due to trauma, inflammation, neurological and musculoskeletal disorders participated in the 8 clinical studies. No serious adverse events were reported to have occurred by any of the study participants.

On April 3, 1972 the agency issued to the sponsor a nonapprovable letter due to deficiencies related to the design of the bioavailability study. On review, the application was found to be unacceptable, since there was inadequate data necessary to support the efficacy of the 500 mg dosage form. The sponsor was also asked by agency representatives to provide statistically significant dose-response data generated from well controlled studies that supported the analgesic superiority of the 500 mg formulation when given at 1000 mg doses as compared to 650 mg doses of the 325 mg strength tablet.

This NDA was resubmitted by the sponsor on December 19, 1972 containing data generated from a new bioavailability study and the results from 4 double-blind, placebo controlled, post-partum pain studies that evaluated the effectiveness of two 500 mg capsules (1000 mg APAP) as compared to two 325 mg tablet (650 mg APAP) in a total of 338 patients. Two out of the 4 studies reviewed demonstrated that a single dose of 1,000 mg of APAP was significantly more efficacious than a single dose of 650 mg of APAP in relieving post-episiotomy pain at 4 hours. Of the remaining 2 studies, one failed to demonstrate a difference in dose response between the 2 doses of APAP while the other study failed to show separation of the active treatments from placebo. The medical officer's review attributes the results of the latter 2 studies to the fact "...that APAP has been demonstrated in many studies as an effective mild analgesic-antipyretic." The overall safety profile of the 1,000 mg dose was also noted to be similar to that of the 650 mg dose with the exception of a higher incidence of dizziness reported to be associated with the high dose by patients enrolled in the clinical trials. Review of the biopharm studies demonstrated that the peak plasma levels for the 1,000 mg dose were not significantly different from the 975 mg dose. Although there was no mention of hepatotoxicity in the animal studies submitted in support of this NDA, the pharmacology reviewer did note in his discussion that there was "...evidence that APAP potentiates the effects of anticoagulation on the prothrombin times in plasma," and recommended that this should be kept in mind when the product was given in combination with salicylates. This application was subsequently approved on May 15, 1973 after the sponsor agreed that it should be available as an OTC product given the marketing history of the 325 mg tablet.

On July 22, 1975 NDA for a 500 mg tablet immediate-release formulation of APAP was approved by the agency for the OTC market (NDA 17-552 Extra Strength TYLENOL® 500 mg APAP tablet). The summary basis of approval for this 505(b)(2) application was the data generated from two crossover bioequivalence studies which compared two 500 mg tablets (1,000 mg) to two 500 mg capsules of APAP. The pharmacology review of this application contains references of recently published articles from the literature which discuss APAP-associated hepatotoxicity in animal models who had been primed with drugs that induce metabolizing enzymes. This resulted in a labeling recommendation for a consumer warning on APAP-containing products regarding the prolonged use of high doses of APAP associated with the ingestion of coffee, alcohol, barbiturates, or other enzyme inducing substances.

With the publication of the TFM in 1988, the 500 mg strength, single-ingredient, immediate-release APAP was marketed under the monograph system. (Note: The capsule formulation is no longer marketed in the U.S. due to the potential risk of product tampering.) This document addresses public comments that had been submitted to the docket in response to the liver warning recommended by the 1977 Expert Panel for APAP-containing products. The TFM states that the agency tentatively decided not to include the Panel's recommended warning regarding APAP-associated hepatotoxicity since it was felt consumer warnings should not include information about organ specific toxicity that was due to a deliberate acute drug overdose. The document also contains an extensive discussion about the data that was then available in support of a warning for hepatotoxicity associated with the chronic use of APAP (i.e., longer than 10 days). The agency concluded that there was insufficient evidence to support a labeling warning for hepatotoxicity secondary to chronic APAP usage.

II. 650 mg Sustained-Release (SR) APAP

The 650 mg sustained-release (SR) formulation of APAP is the only formulation marketed in the U.S. that is currently not regulated by the monograph process. NDA 19-872 for TYLENOL® Extended Relief was approved by the agency on June 8, 1994. The 505(b)(2) application for this formulation had been filed originally with the agency in 1988 and contained the results from 3 bioequivalence studies. Due to the lack of adequate bioequivalence data and clinical trial data to support approval, the agency refused to file the application in July 1988. It was subsequently withdrawn by the sponsor in 1992, and was later resubmitted for agency review with data from 4 bioequivalence studies and the results generated from 3 clinical analgesic studies. Two of the clinical studies were double-blind, placebo-controlled, single-dose clinical analgesic studies in 120 dental and 120 post-episiotomy pain patients which compared the analgesic efficacy of a single-dose of SR APAP to that of 2 doses of immediate-release APAP. Although the dental pain study demonstrated that both formulations were comparable in analgesic efficacy, the results from the post-episiotomy study were confounded by a large placebo response. The third study was a double-blind, uncontrolled, multicenter, multidose, 30-day, osteoarthritis post-flare-pain study which evaluated the analgesic effectiveness of 3,900 mg/day in divided doses of SR APAP to that of 4,000 mg/day in divided doses of immediate-release APAP in 197 patients. Since this study was not a placebo-controlled study, the medical reviewer concluded that the study's results could only be used as indirect evidence in support of SR APAP in the treatment of osteoarthritis pain and its comparable efficacy to immediate-release APAP in the treatment of this condition. Review of the 3 bioequivalency trials revealed that SR APAP was bioequivalent to the approved APAP formulations tested. The safety profile of SR APAP was found to be similar to that of the immediate-release formulation used in these studies. All reported adverse events associated with the product were of minor consequence and indistinguishable from concurrent illnesses.

In addition to the above clinical trial data, the sponsor submitted the results from an extensive literature search on APAP-induced hepatotoxicity. A required alcohol warning for all APAP-containing products was subsequently adopted by the agency in 1998.