of the nature and degree of risk now known to be associated with DPX use and abuse. In addition, the Secretary ordered FDA to hold a public hearing on the effectiveness, modes of use, and safety of DPX, and to conduct and complete a comprehensive study of the scientific data on DPX.

Highlights of material being studied by FDA are summarized in the following sections on "efficacy studies" and "safety".

EFFICACY STUDIES

Propoxyphene

1. *Early studies on DPX seemed to establish that the drug was an effective, though mild, analgesic.*—This was demonstrated by the conclusion of the NAS/NRC Panel on Drugs for Relief of Pain (Ref. 2). The chairman of the panel was Louis Lasagna, M.D., and expert in the field of clinical pharmacology and analgesia. William T. Beaver, M.D., a member of the panel and also an expert in the field of analgesia, concluded as follows in 1966: "In summary, dextropropoxyphene is a mild oral analgesic which is of questionable efficacy in doses lower than 65 milligrams. The drug is definitely less potent than codeine, the best available estimates of the relative potency of the two drugs indicating that dextropropoxyphene is approximately ½ to ⅔ as potent as the latter drug. Likewise, dextropropoxyphene in 32 milligram to 65 milligram doses is certainly no more, and possibly less, effective than the usually used doses of aspirin or A.P.C." (Ref. 3).

2. *Further reviews of 1970 and 1972 confirmed previous views of DPX as effective for mild to moderate pain.* The methodology for the clinical assay of analgesic efficacy was less sophisticated at that time, however, and many of the early studies would not meet today's criterial as adequate and well controlled (21 CFR 314.111). Thus, in a review paper published in 1970 by Miller et al., less than 10 percent of the published reports of DPX hydrochloride that were reviewed consisted of double-blind placebo comparisons. Miller cited 9 of 18 placebo-controlled trials in which DPX was more effective than placebo and concluded that "Propoxyphene is no more effective than aspirin or codeine and may even be inferior to these analgesics * * * When aspirin does not provide adequate analgesia it is unlikely that propoxyphene will do so" (Ref. 4). Prior to the 1972 labelling changes. Dr. Beaver again reviewed for FDA the published scientific literature on DPX products and concluded that they were effective (Ref. 5).

At the time of these reviews, it appeared that most of the studies that did not demonstrate efficacy showed significant methodological problems or lack of assay sensitivity in that they were unable to distinguish between a codeine or aspirin "standard" and placebo. However, some recent studies have *not* shown these problems; they appear adequate and well controlled and repeatedly demonstrate the efficacy of other analgesics but have not done so with DPX.

3. *Three recent "negative" studies are cited in the HRG petition.*—The first is a 1972 study by Moertel et al., in which DPX was compared to other marketed analgesics and placebo in a single-dose trail in cancer patients. DPX, ethoheptazine, and promazine were not superior to placebo in the relief of pain. Aspirin (650 mg) was found to be the most effective agent, followed by pentazocine, acetaminophen, phenacetin, mefenamic acid, and codeine (Ref. 6).

Hopkinson et al. in a study reported in 1973, compared single doses of DPX hydrochloride (65 mg), acetaminophen (650 mg), DPX plus acetaminophen, and placebo in 200 patients with postepisiotomy pain and found that DPX was statistically no better than placebo in the relief of pain (Ref. 7).

Gruber, in a two-dose study in 46 patients, compared DPX napsylate (50 to 100 mg) to codeine (30 or 60Mg) and placebo. He found that although there was no measurable difference betweeen either active drug and placebo after the first dose, both drugs were superior in effect to placebo after the second dose (the drugs were not significantly different from each other) (Ref. 8).

4. *Not all recent reports are negative.*—A 1978 study by Sunshine et al. found DPX napsylate at 200 mg (twice the recommended dose) to be significantly better than placebo. The lowest dose used (50 mg) was slightly better than placebo, but the usual dose (100 mg) was not tested (Ref. 9). These reports reinforce the conclusions of Beaver in 1966 that the results of DPX efficacy studies "of apparently suitable design . . . are to a degree contradictory" (Ref. 3).

In a second review by Miller in 1977, three studies showed DPX to be no more effective than placebo, and in five other DPX was as effective as the standard