third of the prescriptions, but experience roughly half the deaths. If propoxyphene-associated deaths were predominantly accidental, one would expect a much higher proportion of the deaths to occur among users over 60, assuming that older users are at least as likely to have fatal accidents as younger users.

The only serious health risk from propoxyphene other than the deaths described above is that the drug can cause physical dependence. Otherwise, it does not cause significant adverse reactions in many cases. Miller and Greenblatt (ref. 3 found that adverse reactions in hospitalized patients are infrequent and mild. Moreover, although the adverse reactions from propoxyphene that did occur were qualitatively similar to those from codeine and other analgesics used in the hospital setting, they occurred less frequently. Standard tolerance studies in volunteers revealed no significant difference between propoxyphene and placebo. In contrast, Goodman and Gilman (ref. 4 state that in equianalgesic doses, propoxyphene and codeine may be expected to produce similar incidences of side effects.

Thus, the principal harm posed by propoxyphene, and the basis of the HRG petition, are the deaths associated with the use of the drug in suicide attempts or accidental overdosing or interactions with other nervous system depressants in drug abuse situations.

B. Possible Harm From Immediate Suspension of Propoxyphene From the General Market

The principal harm from immediate suspension of a drug is the loss to patients of the benefit of its therapeutic effectiveness. Therefore, to assess the harm from suspension of propoxyphene, it is necessary to evaluate the available information concerning its effectiveness.

I recognize that the efficacy of analgesics is particularly difficult to assess. Pain is a subjective symptom. I am informed that although it can be quantitatively measured for purposes of clinical trials, the conduct of such trials is complicated by the fact that any analgesic will have a large placebo effect, typically in the range of 30–35% of the patients. In addition, many experts believe that in the case of prescription analgesics, such as propoxyphene, the placebo effect associated with the drug is increased by the facts that the drug is prescribed by a physician after consultation with the patient, that the capsules and tablets are colored rather than white, and that the drug is dispensed by a pharmacist.

Moreover, the overwhelming majority of prescriptions for products containing propoxyphene are for compounds containing it in combination with another analgesic, such as aspirin or acetaminophen. These combinations are clearly effective because of these other analgesics, and propoxyphene may make an additional contribution to their efficacy.

The literature on the efficacy of propoxyphene itself is mixed. HRG gives major attention to a literature review conducted by Miller *et al.* in 1970 (ref. 5). Miller cited 9 of 18 placebo controlled trials in which propoxyphene was found to be more effective than the placebo. Miller concluded that "[p]ropoxyphene 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." HRG also cites three subsequent studies that found no significant difference between propoxyphene and placebo. On the other hand, a 1978 study by Sunshine *et al.* (ref. 6) found propoxyphene napsylate at 200 mg (twice the recommended dose) to be significantly better than placebo. The lowest dose used (50 mg) was slightly better than a placebo. The usual dose (100 mg) was not tested. In a second review of the literature in 1977, Miller (ref. 7) reported that three studies showed that propoxyphene is no more effective than a placebo and that five studies showed that it is as effective as (but not more effective than) a standard analgesic.

For purposes of this preliminary assessment of propoxyphene's efficacy in reaching an imminent hazard determination, I conclude that propoxyphene has some, but limited, efficacy.

Thus, it is possible that there may be some risk to patients who do not adequately respond to (or, in relatively few cases cannot safely take) aspirin, acetaminophen, or other analgesics, and who would be deprived of propoxyphene. Moreover, propoxyphene does induce some degree of physical dependence, so that suddent unavailability could lead to withdrawal symptoms for some patients.