propoxyphene meets the criteria for suspension, FDA will immediately submit it to me. I will then consider, in light of that evidence, whether to suspend any or all of the NDA's for propoxyphene products.

Three other steps, described below, will provide information to physicians, dentists, pharmacists, and the general public, in order to increase awareness of the risks of propoxyphene, and may result in the imposition of additional restrictions on the production and distribution of the drug under the Controlled Substances Act.

A. Severity and Likelihood of Harm to the Public Health

The principal harm from propoxyphene is death. As HRG points out, propoxyphene is associated with a significant number of deaths. In 1977, the DAWN system reported 607 propoxyphene related deaths, more than those associated with any other prescription drug.

The DAWN data provide, however, only a very rough basis for estimating the true number of deaths that may be caused by use of propoxyphene. The DAWN reports include all deaths in which propoxyphene is found in the bloodstream of the deceased. In some of these cases, propoxyphene, particularly in conjunction with alcohol or a tranquilizer, may have caused the death. On the other hand, if propoxyphene happened to be found in the blood of a person who died in an unrelated car accident, that case would be reported in the DAWN statistics as a propoxyphene-associated death. The DAWN statistics also do not reflect all of the deaths in the country, but include only deaths in 24 major cities, covering slightly over 30% of the total U.S. population. Thus, it is likely that additional deaths associated with propoxyphene are occurring in areas which are outside the DAWN reporting system.

The absolute number of deaths must be viewed in perspective with the actual consumption of the drug. Propoxyphene is very widely used; last year, about 31 million out-patient prescriptions were filled, and additional quantities of propoxyphene were used in hospitals, clinics, and physicians' offices. The ratio of propoxyphene-associated deaths (i.e., the number of times the drug is mentioned in coroners' reports included within the DAWN system) to dispensed out-patient prescriptions is lower than that for the barbiturates, the non-barbiturate sedative-hypnotics, amitriptyline, doxepin, and pentazocine. In fact, propoxyphene now ranks 12th out of 27 drugs in ratio of drug-associated deaths to dispensed prescriptions.

The reason for these deaths has long been thought to be suicide. Undoubtedly this motivation accounts for a significant proportion of the deaths. In its petition, HRG contends, however, that many of the deaths are the unintended result of drug abuse. The petition appears to suggest that in a search for euphoria, or because of a dependence on the drug, a user may take an excessive dose of propoxyphene or combine the drug with alcohol, narcotics, tranquilizers, sedative-hypnotics, or other substances that depress the central nervous system. The result can be an accidental death.

It is true that most identified propoxyphene-associated deaths appear to be the result of misuse of the drug, either in attempting suicide or in a drug abuse accident. In the report by Baselt *et. al.* (ref. 1), some of the cases classed as "accidental" involved such large quantities of propoxyphene that it is very likely that the drug was not being used for therapeutic purposes at the recommended dosage level.

Since filing the HRG petition, Dr. Wolfe has raised the question whether many of the deaths attributed to propoxyphene are due to a cariotoxic effect of its major metabolite, norpropoxyphene. This hypothesis, which would imply the existence of previously unidentified cases of propoxyphene-caused deaths possibly occurring at therapeutic doses of the drug, deserves serious consideration during FDA's review of the drug. At present, however, there is little evidence that this mechanism is a common factor in the deaths associated with propoxyphene.

Indeed, there is no clear evidence to date demonstrating that the therapeutic use of propoxyphene, in the absence of tranquilizers or alcohol, has caused accidental death. For example, although about one-third of the prescriptions for products containing propoxyphene are written for patients over age 60, these same patients experience only 8% of the deaths reported to be associated with propoxyphene. The largest incidence of deaths associated with propoxyphene products occurs among those in the 20–40 age range, who only receive about one-