Other patients who depend particularly on propoxyphene for relief from pain may experience some suffering as the result of the abrupt removal of the drug from the market. For these people, the most likely substitute for propoxyphene is codeine, which is widely believed to be even more addictive than propoxyphene. If presented with the sudden disappearance of propoxyphene from the market, physicians would still be reluctant to prescribe codeine for more than intermittent use, and patients would be reluctant to take it.

C. Likelihood of Final Action to Withdraw the Drug from the General Market[2]

The Bureau of Drugs in FDA has responsibility for initiating a withdrawal proceeding (21 CFR 314.200), but has not proposed that the NDA's for propoxyphene be withdrawn. Possible grounds for withdrawal of these NDA's include (1) that evidence from clinical experience shows the drug to be unsafe, (2) that new evidence not available when the NDA's were approved, together with the original evidence supporting the approvals, demonstrates that the drug is no longer shown to be safe, and (3) that the new evidence, evaluated together with the evidence in the original NDA's, supports a finding that there is a lack of substantial evidence that the drug is effective. 21 U.S.C. 355(e) (1), (2), and (3).

The issues concerning the safety and effectiveness of propoxyphene are difficult and complex.

Although the drug is associated with a large number of deaths, many of these deaths appear to be related to misuse of the drug rather than its use in accordance with the labeling directions. It is not clear that many of these deaths—those related to suicide attempts—would be prevented if propoxyphene were immediately removed from the market.

In addition, the record currently does not contain sufficient evidence for me to make a finding of imminent hazard based on two as yet unresolved issues raised by HRG's petition:

(*1*) The extent to which propoxyphene is dangerous, if at all, when used in accordance with the labeling;

(*2*) The extent to which labeling restrictions are effective in controlling use of propoxyphene that may lead to death.[3]

On the basis of the information with respect to propoxyphene available to me at this time, I cannot conclude whether or not one or more of the new drug applications is likely to be withdrawn. That determination cannot be made until the issues concerning the efficacy and safety of propoxyphene in light of all the data now available have been developed more fully.

D. Potenial Alternative Means To Prevent Hazard

During the period FDA is evaluating further the safety and efficacy of propoxyphene, three steps can be taken to protect the public health. I am concerned by the various dangers posed by propoxyphene; use in suicides, accidental deaths from the interaction of the drug with alcohol or other drugs that act on the nervous system, and dependence on the drug. Therefore, I am directing that these problems be addressed immediately without awaiting the final FDA decision on whether propoxyphene meets the statutory standards of safety and effectiveness. I believe that implementation of the following actions will reduce the hazards to the public health.

First, the Department will promptly evaluate HRG's proposal to transfer propoxyphene from Schedule IV to Schedule II of the Controlled Substances Act. If this transfer were made, the production of propoxyphene would be limited by government-determined quotas; all distribution of the drug would be on special order forms; and prescriptions for the drug would not be refillable and would have to be in writing (i.e., telephone prescriptions would be prohibited). The Assistant

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[2] Because final responsibility for deciding whether the new drug applications for propoxyphene should be withdrawn is delegated to the Commissioner of Food and Drugs, I have not asked Dr. Kennedy to comment on this matter, and he has reserved judgment until formal administrative procedures have developed a complete record for his review.

[3] In the phenformin case, the evidence did support a finding that phenformin was dangerous even if used in accordance with the labeling. In addition, the evidence showed that phenformin was being used widely outside of the indications set out in the labeling.