This guidance was written prior to the February 27, 1997 implementation of FDA's Good Guidance Practices, GGP's. It does not create or confer rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. This guidance will be updated in the next revision to include the standard elements of GGP's.

August 2, 1990

FDA Guidance to Firms on Biliary Lithotripsy Studies

To establish the safety and effectiveness of lithotripters used in the treatment of patients with symptomatic gallstones, it must be shown in adequate and well-controlled studies that a clinical benefit results from the lithotripsy. This benefit is achieved when the gallbladder does not often free itself of stone fragments, and adjunctive treatments are used to eliminate the gallstone fragments that are produced by lithotripsy. Most investigations of biliary lithotripsy in the United States have used ursodiol as the adjunctive treatment; other studies have used chenodeoxycholic acid. These studies have shown that the combination of treatments can clear the gallbladder of stones in a fraction of the patients treated, but results of studies of a combination of lithotripsy and ursodiol, without an ursodiol control group, are difficult to interpret, as ursodiol itself will dissolve stones. These studies, therefore, do not demonstrate a contribution of the lithotripter to the observed elimination of gallstones from the gallbladder. Note that it is possible that studies using lithotripsy alone in specific populations might show effectiveness of that procedure if success rates were adequate in light of risks.

FDA had hoped that the data from studies supporting the approval of ursodiol (Actigall) could be accessed and used to provide a historical ursodiol control for comparison to the effects of lithotripsy with ursodiol. CDER officials familiar with the existing Actigall data base, however, have concluded that it is unlikely to represent a satisfactory historical control. Dissolution rates are highly variable in different populations, and it would be difficult to conclude that a historical series contained patients comparable to the contemporary lithotripsy/ursodiol group. It would also be difficult to be sure that adverse effect assessment was similarly evaluated in the two sets of trials. Attempts by lithotripter manufacturers to develop this historical ursodiol data base as a control have in fact been unsuccessful.

FDA therefore recommends that lithotripter manufacturers studying biliary lithotripsy in conjunction with ursodiol add an ursodiol-only control arm to their on going studies. The comparison of and unequivocal assessment of the contribution of lithotripsy and will compare the overall safety of the two therapeutic approaches

(ursodiol alone vs. lithotripsy/ursodiol). PMA applications for biliary lithotripsy will need to include data from such studies.

CDRH will review PMA's for the lithotripters for biliary use and will consult with scientific staff at CDER during the review.

Before lithotripter labeling can recommend adjunctive use of ursodiol, labeling for ursodiol must include the new indication: "adjunctive use with lithotripsy to dissolve gallstone fragments" (or some close variant). While we recognize that this does not represent a use totally different from the current approved use, gallstone dissolution rates are very variable, depending on the size, number, and calcium content of stones, and labeling to date has been very specific about the precise conditions of use. The adjunctive use would represent a major increase in the number patient likely to be treated. It is therefore necessary to show that in the adjunctive setting, ursodiol contributes to the gallbladder clearing effect of lithotripsy and that this occurs without unacceptable new risks. The most direct way to show this would be a trial comparing lithotripsy/ursodiol with lithotripsy alone; indeed such studies as there appears to be data, both available in full detail (with case reports) and in the literature, showing that lithotripsy could be provided by a manufacturer of ursodiol in a supplement to an existing ursodiol NDA or as part of an NDA for a new product. It could also be provided by one or more lithotripter manufacturers in a master file, and permission given to FDA to utilize the data on behalf of one or more ursodiol manufacturers to support a labeling supplement. We are prepared to accept data derived from use of any ursodiol preparation as applicable to another preparation of comparable bioavailability.