Questions for Gastrointestinal Drugs Advisory Committee
Chemoprevention of Sporadic Colorectal Cancer (CRC)
March 19, 2002

1) For individuals who are able and willing to undergo colonoscopic screening or surveillance, is either partial and/or complete suppression of colorectal adenomatous polyps a clinically meaningful benefit? Why or why not?

   If adenomatous polyp suppression is not a clinically meaningful benefit, what additional information would be needed to demonstrate that partial or complete suppression of polyps is of clinical benefit in such individuals?

2) A chemoprotective agent (CPA) that suppresses polyp growth may become resistant to drug effects. Additionally, it may preferentially allow small, invasive lesions to go undetected on colonoscopy while large, indolent lesions are identified and removed. If polyp suppression is used as an endpoint in clinical trials of a CPA:

   a) How long should the trial be?
   b) What should the time interval be between colonoscopic evaluations?
   c) What endpoints and follow up are needed to rule out possible resistance to drug effects? Differential identification and removal of large, indolent lesions?
   d) How should a rebound withdrawal effect be studied?

3) Given that mortality and invasive CRC incidence rates are gold standards for demonstrating clinical benefit, what is the relative importance of other study endpoints in clinical trials of CPAs, such as:

   a) Lengthening the interval between (or replacement of) colonoscopic screening or surveillance?
   b) Reduction in the number of procedural complications associated with polypectomies?
   c) Other clinically meaningful outcomes?

4) Should the results of clinical trials in individuals at high risk for CRC be generalized to individuals at normal risk for CRC? Why or why not? Please specify the criteria that should be used to classify risk in clinical trials of CPAs.

5) Should clinical trials of CPAs be required to include substantial numbers of individuals with particular demographic or baseline characteristics (e.g., age, race, sex) or on particular concomitant therapies (e.g., nonsteroidal anti-inflammatory agents)?

(GI Advisory Committee Questions Cont'd)

6) In randomized, placebo-controlled clinical trials of CPAs used as an adjunct to colonoscopic screening or surveillance, what would represent a clinically meaningful effect size for:
   a) Reduction of benign adenomas?
   b) Reduction of premalignant lesions?
   c) Reduction of colorectal cancer?
   d) Increase in the time interval between colonoscopies?
   e) Reduction of complications associated with polypectomies?

7) How should dropouts/censored patients be analyzed?

8) What is your advice concerning the safety evaluation of a drug proposed as a CPA in an at-risk population without active disease?

9) For partial or complete suppression of adenomatous polyps:
   a) Should the proportion of patients who experience the clinically meaningful benefit of polyp suppression exceed the proportion of patients who experience serious adverse events?
   b) If yes, should the study be powered accordingly? Why or why not?
   c) In order to ensure long term safety of CPAs, what should the length of the clinical trials be?