Questions for the Committee:

- Adequacy of Clinical Data to Support Effectiveness
- *In general, the FDA requires an Applicant for a new drug product to submit two adequate and well-controlled clinical trials as substantial evidence of effectiveness. One of the circumstances in which a single clinical trial may be used as substantial evidence of effectiveness is a trial that has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with a potentially serious outcome, and confirmation of the result in a second trial would be logistically impossible or ethically unacceptable. The Applicant is seeking marketing approval for 17-hydroxyprogesterone caproate (17OHP-C) based primarily on (1) the findings from a single clinical trial and (2) a surrogate endpoint for neonatal/infant morbidity and mortality (i.e., reduction in the incidence of preterm births at less than 37 weeks gestation).*

Question 1:

- 1a. Is the primary endpoint of Study 17P-CT-002 — prevention of preterm birth prior to 37 weeks gestation — an adequate surrogate for a reduction in fetal and neonatal mortality or morbidity?

Question 1:

- 1b. If not, would prevention of preterm birth prior to prior to 35 weeks gestation be an adequate surrogate?

Question 1:

- 1c. If not, would prevention of preterm birth prior to 32 weeks gestation be an adequate surrogate?

Question 2:

- 2. Do the differences in the incidence of preterm birth in Study 17P-CT-002 prior to 37 weeks in the vehicle (control) group (55%) compared to those in the control arms of (a) another Maternal Fetal Medicine Units Network trial (approximately 37%) and (b) Study 17P-IF-001 (36%) evaluating similar high risk populations indicate the need to replicate the findings of Study 17P-CT-002 in a confirmatory trial?

Question 3:

- 3a. Do the data reviewed by the Committee provide substantial evidence that 17OHP-C prevents preterm birth prior to 35 weeks gestational age?

Question 3:

- 3b. Do the data reviewed by the Committee provide substantial evidence that 17OHP-C prevents preterm birth prior to 32 weeks gestational age?

Question 3:

- 3c. Do the data reviewed by the Committee provide substantial evidence that 17OHP-C reduces fetal and neonatal mortality or morbidity?

- **Potential Safety Concern and Adequacy of Safety Data**
- ***There was a numeric increase in the percentage of second trimester miscarriages (pregnancy loss prior to Week 20 of gestation) and stillbirths in the 17-hydroxyprogesterone caproate group. Overall, 11 of 306 subjects (3.6%, 17OHP-C group) and 2 of 153 subjects (1.3%, vehicle group) had a second trimester miscarriage or stillbirth.***

Question 4:

- **4a. Is further study needed to evaluate the potential association of 17OHP-C with increased risk of second trimester miscarriage and stillbirth?**

Question 4:

- 4b. If so, should this information be obtained prior to approval for marketing or post-approval?

Question 5:

- 5. Are the overall safety data obtained in Studies 17P-CT-002 and 17P-IF-001 and Study 17P-FU (long-term follow-up) adequate and sufficiently reassuring to support marketing approval of 17OHP-C without the need for additional preapproval safety data?

Question 6:

- 6a. If 17-hydroxyprogesterone caproate were to be approved for marketing without additional preapproval clinical studies, would you recommend that the Applicant conduct a post approval clinical trial(s) to investigate further safety or effectiveness?

Question 6:

- 6b. If so, what would be the primary objective of the trial(s) (i.e., what unanswered question(s) would the study investigate)?