April 30, 2003

Via Fax and UPS

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 03D--0001
Draft Guidance for Industry – "Nonclinical Safety Evaluation of Pediatric Drug Products"; FR # 22 – Volume 68, February 3, 2003

Dear Sir/Madam:

Aventis Pharmaceuticals is pleased to provide the following comments on the above-referenced draft guidance entitled, "Nonclinical Safety Evaluation of Pediatric Drug Products". This draft guidance provides recommendations on the role and timing of animal studies in the safety evaluation of therapeutics intended for the treatment of pediatric patients.

IV. B. 2. Age (of the animals)
Aventis suggests the following addition to consider the case of the premature newborn: It is suitable to evaluate embryonic and fetal animal data (embryo-fetal toxicity studies and pre-postnatal developmental toxicity study) for premature newborn assessment.

IV. C. 3. Dose Selection (page 9): frank toxicity
The recommendation "The high dose should produce frank toxicity, developmental or general" does not support the aim of the detection of developmental organ toxicity. This statement stems from the traditional way of looking at adult toxicity studies. Toxicity in juvenile studies should not be evaluated the same as a general toxicity studies first because treatment of pups is an ethical issue and second because these studies are coming as additional studies after the general and reproductive toxicology packages. Aventis suggests the following change "The high dose should produce *minimal* toxicity, developmental or general" as expressed in the note 7 of the ICH Reproductive toxicity guideline.

IV. C. 3. Dose selection (page 9): high dose selection

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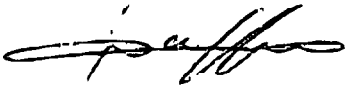
Based on the previous comment, Aventis suggests the following process for high dose selection: If the juveniles are more sensitive there is less probability of killing the animals with the approach suggested above than with a severely toxic high dose approach. If the juvenile were to be less sensitive then the issue of differing sensitivities would be resolved since the adult therapeutic dose could be used.

VI. A. Nervous system (page 12)
The reference No 3 did not refer to the ocular dominance.

VI. B. Reproductive system (page 12)
The onset of sexual maturity is considered to be closer to 70 days rather than 100 days as expressed in the review Ojeda S.R. and Urbanski H.F. (Puberty in the rat, *in* The physiology of reproduction [Raven Press Ltd., New York] Knobil E. and Neill J.D., 1699-1737, 1988). On the other hand, Eckstein B. et al. (Onset of puberty in the immature female rat induced by 5alpha-androstane-3beta, 17beta-diol. Endocrinology, 1973; 92: 941-945) also showed that the first estrus appears earlier in rat, i.e., at 36 days of age with the vaginal opening.

On behalf of Aventis Pharmaceuticals, we appreciate the opportunity to comment on the "Nonclinical Safety Evaluation of Pediatric Drug Products" draft guidance and thank you for your consideration.

Sincerely,



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