



ABBOTT LABORATORIES

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

Ref: Docket No. 99N-2079, CDER 2001100. Draft Guidance for Reviewers on the Integration of Study Results to Assess Concerns About Human Reproductive and Developmental Toxicities.

Abbott Laboratories is very pleased to have the opportunity to provide comments on the Draft Guidance for Reviewers on the "Integration of Study Results to Assess Concerns About Human Reproductive and Developmental Toxicities" published in the Federal Register on November 13, 2001.

We thank the Agency for your consideration of our comments. Should you have any question, please contact Ivone Takenaka at 847-935-9011 or by FAX at 847-938-3106.

Sincerely,

DL Sporn by RPhu

Douglas L. Sporn

99N-2079

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**Abbott's comments on the
Draft Guidance for Reviewers on the
Integration of Study Results to Assess Concerns About
Human Reproductive and Developmental Toxicities**

DOCKET No. 99N-2079

COMMENTS

Section II.B.2. Developmental Toxicities

• **Lines 137-141 - Dymorphogenesis**

Clarification is needed regarding the distinction between strong versus weak signals. For example, in the dymorphogenesis category, malformation and variations are both regarded as structural alterations.

Section III.C.2.b. Signal Strength, Part II

• **Lines 515-532. Dose-Response Relationship**

We believe the following scenarios may need to be addressed and clarified in the guidance:

- If a positive signal is seen only at the highest dosage in a study, the possibility of a dose-response relationship exists. However, according to the guidance, this does not fall into one of described characteristics and would be considered unchanged or decreased concern.
- Another scenario is the observation of low incidence of adverse effects at all dosages in a study when the dosages were not placed far apart. According to the guidance, this may also be considered as a lack of dose-response according to the criteria.

Section III.C.2.c. Pharmacodynamics

• **Lines 555-587. Therapeutic Index**

With few (usually 3-4) dosage groups and adverse effects generally occurring at the top 1-2 dosages, the TD₁₀ can rarely be determined in toxicology studies. We suggest that it would be more meaningful to calculate the therapeutic index based on a no-toxic-effect dose

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