

Wyeth Pharmaceuticals

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Date: August 8, 2005

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

Re: Docket No. 2005D-0203: June 6, 2005 (70 FR 32839)

Dear Sir/Madam:

Wyeth Pharmaceuticals is submitting the following comments on the FDA's draft guidance for industry entitled, "Safety Testing of Drug Metabolites" (June 2005).

Wyeth is one of the largest research-based pharmaceutical and healthcare products companies and is a leading developer, manufacturer and marketer of prescription drugs, biopharmaceuticals, vaccines, and over the counter medications.

Wyeth appreciates the opportunity to comment on the above-mentioned draft guidance; our comments are provided below

Comment 1

- The scope of the draft guidance appears too broad, and as currently written, would increase the non-clinical testing requirements for many drugs in development. We recommend that the scope be better defined to include only unique human metabolites that are greater than or equal to 10% of the dose, or, preferably, 10% of the systemic exposure to drug derived material (see below), be considered for testing in additional studies.

Throughout the draft guidance, there is an ambiguity about what metabolites need to be tested in additional studies. We propose that it be clarified and defined as pertaining to unique and major human metabolites. Since the exaggerated dose used in animal toxicity studies usually allows for an increased amount of the metabolite to be tested on an amount per kg basis in the animal as compared to a human, the proposed definition should not include metabolites that are produced at a lower percent of the administered dose in animals as compared to humans.

Furthermore, it is recommended that the definition of "major" be based on circulating concentrations of the drug, expressed either as percent of drug derived material, or, until the radiolabeled human ADME study is conducted,

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based on a comparison of the amount of metabolite produced in animals to the amount produced in humans (i.e., AUC). It should not be assumed that metabolites in excreta are representative of systemic exposure because in some cases only excretory organs are exposed to metabolites observed in excreta. Current analytical technologies permit the evaluation of systemic exposure to major metabolites in the vast majority of cases. As is stated in the draft guidance, each situation should be evaluated and discussed with the Agency on a case-by-case basis.

Comment 2

- In the draft guidance (section III.A.), it is stated that one of the objectives of standard nonclinical safety studies is to assess the potential for genotoxicity in support of phase 1 safety and tolerability studies in humans. However, unique or major human metabolites are often not identified until human in vivo metabolism studies are completed. It is therefore recommended that the wording be modified to indicate that assessment of potential genotoxicity be determined after a major human metabolite has been identified in vivo.

Comment 3

- There is inconsistency in the draft guidance regarding general toxicity evaluations in 1 versus 2 species (rodent and non-rodent versus the most appropriate species). For clarity, we recommend that toxicity be evaluated in the species that will maximize the potential to detect the toxicity of the compound, and that it may be acceptable to perform this assessment in a single species.

Comment 4

- Direct dosing of the metabolite (as recommended in section III.A.) by the intended clinical route may likely result in additional and different metabolites not seen after dosing with parent and will result in different pharmacokinetic profiles and tissue distributions that are not reflective of what would be observed when the metabolite is formed from the parent.

Therefore, it is recommended that whenever possible, metabolite toxicity evaluations be performed in a species that produces the human metabolite even if exposure is only equivalent to that observed in humans.

Comment 5

- In the draft guidance (section IV.A.), it is recommended that doses of the metabolite be administered to elicit frank toxicity or be a maximum feasible dose of 2000 mg/kg. However, direct dosing of a metabolite to elicit frank toxicity or to a limit dosage will generally represent exposure multiples that are unrealistically high and may be greater than exposure ratios of parent drug.

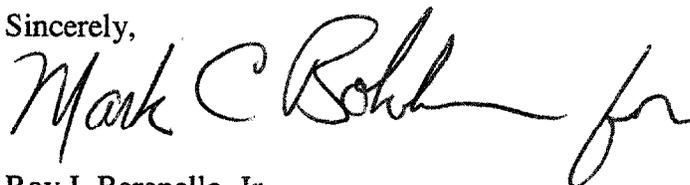
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Furthermore, dosing at high levels up to limit dosages will likely introduce new impurities at potentially toxicologically relevant levels that are not present in the parent drug batches. For human metabolites produced endogenously in animals, but at lower levels, dose escalation of parent drug can generally provide adequate multiples of both the parent and metabolite, which is consistent with the following statement that appeared earlier in the guidance (section III.B.): "If the systemic exposure in nonclinical species is equivalent to human exposure when measured in plasma and/or excreta, levels may be considered sufficient and alleviate the need for additional toxicity testing."

It is therefore recommended that the wording be modified as proposed in Comment 4. (See above.)

We are submitting the enclosed comments in duplicate. Again, Wyeth appreciates the opportunity to comment on the above-mentioned draft guidance, and trusts that the Agency will take these comments into consideration.

Sincerely,



Roy J. Baranello, Jr.
Assistant Vice President,
Worldwide Regulatory Affairs