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Bruce Stadel, M.D.
10827 Deborah Drive
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Dear Bruce:

I reviewed Hoffmann-LaRoche's acutane proposal and have the following comments.

1) The idea of enrolling women through the prescribing physician's office seems very cumbersome. I realize the potential value of the educational impact for both physicians and patients in this model, but it is unlikely to be feasible. It is potentially too disruptive of physicians' practices.

2) There are no denominators of physicians or patients. There is no way of knowing what kind of selection factors or biases enter the study.

The Roche proposal acknowledges these problems. It does not have a solution for them.

With regard to your questions:

1) The study does not obtain these data.

2) Volunteers are likely to be more conscientious than nonvolunteers.

3) The follow-up calls and questionnaires are an intervention that may influence compliance in reporting.

The major issue is how to design a study that does not rely on volunteer physicians and patients. In this regard, I do not know what options the FDA has available to it. If prescribing of

acutane to reproductive age women could be limited only to physicians who would agree to certain kinds of record keeping, then a useful study could be designed. Records would need to be kept of all women in the practice who have the relevant indications for acutane use. This number would provide a denominator. Then one would further need to know which among these were offered acutane, and who accepted and refused, along with follow-up information on those who accepted. Follow-up should also be obtained on a sample of those who refused and those who were in the denominator but were never offered acutane. A non exposed comparison group is necessary.

I did wonder what the medico-legal implications are for Hoffmann-LaRoche or prescribing physicians if a woman using acutane gets pregnant. It would seem to me that it is very risky for both the doctor and the company.

In reading your letter, I was wondering if there are any data on malformation risk in the event a women does get pregnant. Note the enclosed article from the Durham Morning Herald. I have no idea as to the accuracy of this report. But I sense that the Hoffmann-LaRoche proposal may be totally inadequate, given the current media scene, as well as from a scientific standpoint.

Sincerely,

Barbara

Barbara S. Hulka, M.D., MPH
Kenan Professor and Chair

BSH/vmr
Encl.