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PREVENTIVE MEDICINE
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October 14, 1988

Bruce V. Stadel, M.D., M.P.H.
Division of Epidemiology and Surveillance
Office of Epidemiology and Biostatistics
Food and Drug Administration
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Dear Dr. Stadel:

This letter responds to your October 7th request for comments on a protocol for a survey of Accutane use in women, prepared by the Slone Epidemiology Unit (SEU). Before proceeding with my assessment, I should state my high regard for work done by the SEU. It has a distinguished record of epidemiologic research, scientific integrity, and thoughtful analyses and interpretations of studies.

The SEU's tradition of outstanding work and scientific integrity is reflected in its forthright discussion of some of the likely sources of bias resulting from the proposed study. This leads me to believe that if the SEU had full discretion over the survey's design, it would *not* pursue the study as proposed.

Upon reviewing the study protocol, I realized that your cover letter of October 7th raises most of the issues that, in my opinion, make this study not worth doing unless major changes are made.

If one wants a proper assessment of the effectiveness of Roche Dermatologics' efforts to prevent pregnancy in woman taking Accutane, then a study ought to be designed to assure representativeness of the study participants *and* the prescribing physicians. This should be based on either a random sample of women and physicians, or total enrollment. Furthermore, the study should not be an intervention in its own right, so that, when discontinued, the information available to women and the procedures for ensuring that they avoid pregnancy both undergo change.

One problem not addressed by the proposal is that even if a proper study were done, it could only establish that successful efforts to inform women and prevent pregnancy were in place *at the time of study*. What might occur thereafter, when new physicians begin their practices and new sales representatives begin to work for Roche, would be anyone's guess. What is needed, in my opinion, is a non-intrusive study that provides *continued* surveillance of either all prescribing physicians and their patients, or randomly selected samples. This is clearly not possible under the current constraints.

Given the direction of bias resulting from voluntary enrollment in the study - in the direction of overestimating the extent to which women are properly informed of Accutane's teratogenicity, and in the direction of underestimating the pregnancy rate occurring in women while on the drug - the study, as proposed, can only establish *failure* by Roche to achieve its objective: unacceptably high rates of pregnancy or misinformation about Accutane will be underestimates of the actual rates in effect. Unless voluntary enrollment represents 100% enrollment, which is a very unlikely prospect, the study cannot definitively establish even short-term success, by which I mean a successful intervention lasting only for the duration of the survey.

To illustrate the latter point, suppose study enrollment reached 80%, which would be rather high for a survey based on voluntary participation. Further suppose that *all* participating women were properly informed and that *no* pregnancies occurred. What would appear to be an unmitigated success by Roche would still be open to the interpretation that the 20% of women who didn't participate were all poorly informed, and that a substantial fraction of these women were at high risk of pregnancy - the actual number becoming pregnant being completely unknown. There would be no means by which the study could refute these interpretations.

As another apparently successful outcome, suppose that voluntary enrollment reached 100%, that *all* participating women were properly informed, and that *no* pregnancies occurred. Given the fact that the study itself proposes to inform women repeatedly of the risks of Accutane (p.5, p.10), and that the study itself will advise women to stop taking the drug if a survey interviewer determines that a woman is not taking adequate steps to avoid pregnancy (p.20), there will be no way to know what will occur when the study is discontinued. The reasons are first, that the study itself is part of the intervention and second, that new physicians and sales representatives, not covered by the study, will become involved in prescribing and promoting Accutane.

If the study proceeds as planned, it will not resolve the questions it sets out to address. It will only generate data that could very well be misleading, and certainly open to interpretations that are diametrically opposed.

With regard to your question concerning the study's adequacy of documenting the prescribing behavior of physicians, I can only reply that the study protocol does not address this issue.

Sincerely,

James J Schlesselman

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