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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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FROM: Medical Epidemiologist, Epidemiology Branch, HFD-733

SUBJECT: Design considerations for Accutane PMS studies

TO: Chief, Epidemiology Branch, HFD-733

The Agency has instituted a number of regulatory interventions designed to control the problems of Accutane use outside its approved indication and Accutane pregnancy exposure. Reliance has been placed on post-marketing surveillance (PMS) activities to assess the effect of these interventions. In effect, these PMS activities serve as a "safety-valve" or "backstop" to alert the Agency should the regulatory interventions taken fail.

The following pages outline the basic questions of concern regarding Accutane as well as the principles of study design important to reliably answering these basic questions. Finally, a study method incorporating these essential features of study is presented.

The primary questions of importance are: 1) what is the rate of pregnancy exposure to Accutane following regulatory intervention; 2) do patients treated with Accutane fulfill the labeled indication; 3) what is the magnitude of Accutane use among women of childbearing age; 4) who prescribes Accutane; how often, and for what indication; 5) do prescribing physicians adhere to labeled recommendations of Accutane use (ie, only for severe recalcitrant cystic acne, informed consent, pregnancy avoidance counselling, pregnancy testing); 6) what is the knowledge base of patients treated with Accutane; are they fully aware of risks and what measure(s) do they use to avoid pregnancy exposure.

The overriding principle guiding study design is that it provide representative, statistically valid and generalizable results to the questions posed above. Additionally, the study itself should not influence outcome results to the best extent possible. The study should not include interventions which will be discontinued once the study is completed. Data-gathering methods should be as unobtrusive as possible to obtain essential information. Also, provision should be made to monitor/evaluate the duration of effect of these interventions. Physician and patient behavior, as well as pregnancy exposure rates may initially show positive effects which dissipate over time. Therefore, any proposed study must be capable of assessing long-term impact and effect, perhaps through use of several study phases.

There are several reasons why these principles of study design are important. If a statistically unrepresentative subset of Accutane recipients is studied, the results will almost certainly suffer from substantial bias in the direction of showing a positive effect of interventions. Such results will be misleading, and of no practical value because they relate to only a small and unrepresentative subset of physicians and patients. Additionally, if there are features of the study design which serve to inform, educate, or otherwise influence patient or physician knowledge/behavior these features become interventions in their own right. Because the PMS study evaluates the effect of all interventions collectively, they would all need to be continued after study completion as there would be no basis from which to determine which intervention(s) were the essential ones. The study should be unobtrusive because if physicians and patients are consciously aware that they are "under the microscope," their behavior is likely to be influenced toward the desired goal. The study must not of itself bias behavior and outcome measures.

From the above, it is seen that the foundation upon which a valid study is built is the requirement of total registration of Accutane recipients. This will improve the likelihood of obtaining representative, valid, and generalizable results. If the number of Accutane recipients is small, all should be studied. If the number is large, a representative sample obtained via an appropriately designed random sampling technique might be employed. In this latter setting, power considerations and the desired level of confidence in the point estimates would dictate ultimate sample size.

From the design perspective, the issue to be resolved is how best to accomplish total registration of Accutane recipients. Given the nature of the newly implemented regulatory interventions, the manufacturer is in a position to voluntarily achieve this. It is in the manufacturer's and the public's interest that a representative, valid, and generalizable study be performed. Several methods may exist by which total registration is accomplished. One method would be to link receipt of Accutane to registration and participation in the study. This linkage might be accomplished through a program of direct dispensing of Accutane by the treating physician to the particpating patient. Patients unwilling to be study participants would not be dispensed Accutane. In this scenario, the drug would not be available through pharmacies. The manufacturer could ensure physician cooperation by not supplying Accutane to physicians failing to register all recipients. Other approaches are possible. What is important is that this type of approach would probably substantially increase the likelihood that a reliable and generalizable study result was obtained. The larger the degree of incomplete or non-participation by physicians and patients, the greater the likelihood of volunteer bias, and the potentially mistaken impression that Accutane is used only within its approved indication and that pregnancy exposure no longer occurs.

In terms of the questions of concern, this type of study design would provide the Agency with an accurate description (number and demographics) of Accutane recipients. It would also provide the template from which to obtain answers to the other questions. These other questions would require administration of carefully designed, standardized questionnaires, answered by telephone or perhaps by in-person interview. Independent validation of some data could be obtained through review of submitted informed consent forms, and through auditing of a random sample of physcian/patient records.

Questionnaire administration could be arranged in a variety of ways so as to not itself constitute an intervention. If a typical course of Accutane therapy is five months, questions relating to quantitation of pregnancy exposure might be asked at seven months after starting Accutane, or two months after stopping Accutane. Patient knowledge and behavior could also be assessed at this time, as well as a description of the nature, severity, extent and duration of disease for which they received Accutane. Physician practice and behavior could be assessed separately with validation of a subsample using medical records auditing. Because recent publicity in lay and professional media has been great, and because many studies regarding behavior modification have shown that behavior change is often short-lived, provision must be made for additonal study of newly treated patients at some time in the future (perhaps one year or two years hence). Also, because of the nature of the area of study (behavior), specialists in this area should probably be consulted for questionnaire design. Finally, it would also seem prudent that the researchers conducting this study be as independent as possible from influence by the manufacturer.

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cc:
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HFD-733 Chron
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