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DAVID C. BRADFORD, PhD, MPH

PEGUS RESEARCH, INC.

AND

DEPARTMENT OF FAMILY AND PREVENTIVE
MEDICINE,
UNIVERSITY OF UTAH SCHOOL OF MEDICINE

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The interests of public health are better served by supplementing or supplanting the “time and extent of use” standard for assessing safety with data from appropriately designed active safety trials.

ASSUMPTIONS

1. Standard comparative trials have already demonstrated efficacy for the switch candidate in the proposed OTC dose and for the proposed OTC indications.
2. The safety of the drug in prescription use has already been well characterized.
3. The basic question that must be answered in order for the decision to be made about a switch is *whether removing physician involvement in the drug use process (that is, diagnosing the disease, prescribing a drug, and monitoring drug use and outcome) results in an unacceptable increase in public health risk.*

Passive surveillance is inadequate for rate determination because:

1. Voluntary reports from a variety of sources almost certainly contain significant but unknown biases and substantial (but also unknown) underreporting. Therefore, the data which form the numerator in a rate estimate are inadequate.
2. Estimates of drug use, the denominator for a rate, are either missing or flawed. Where sales data are used to estimate the amount of drug use, there is no information about the amount or conditions of use for the persons for whom and adverse event is reported.
3. The amount of information about each case is limited, and there is little or no capacity to query the data to fully evaluate the nature and severity of the adverse event and its relationship to the use of the drug.
4. Reports are of cases of *prescription*, not OTC, drug use. However, the OTC use patterns may be quite different from prescription use in the indications for treatment, the strength and frequency of the dose, and the nature of the patients who self-select for OTC treatment.

DESIGN PRINCIPLES OF AN APPROPRIATE ACTIVE OTC SWITCH SURVEILLANCE STUDY

1. Subjects should be evaluated in a setting that is as similar to the actual conditions of proposed OTC use as possible.
2. Subjects should self-select into the trial (and into the treatment arms of a study which has an active comparator).
3. All subjects who self-select into the trial should be allowed to participate.
4. The study must be open-label, so that the processes subjects use to decide whether and how to use the drug can be assessed.
5. Assessment of drug use and outcome should be unobtrusive, so that the act of measuring doesn't influence the process.
6. Studies should be relatively large, to generate the power to reliably detect rare adverse events (e.g., those with a rate of .001 to .0003).
7. Subject recruitment and enrollment procedures should be as simple and realistic as possible, to produce a sample that is representative of prospective OTC users.
8. Recruitment and enrollment should be done in sites where people go to obtain their OTC medications.

SUMMARY

1. Properly designed safety trials can provide important information which is directly relevant to the question of drug safety in actual OTC use.
2. Active surveillance studies can provide true adverse event rate estimates relatively quickly. Therefore, the decision about a potential OTC switch can be made more quickly and efficiently, with greater accuracy.
3. Active surveillance may be particularly useful for drugs that have a relatively low prescription use rate, a being considered for direct-to-OTC approval, or are on a fast track for OTC approval.