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Comments on the FDA Risk-Management Concept Papers
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My name is Paul Stolley and I am a medical epidemiologist with a special interest in the epidemiology of adverse drug reactions. I currently work part-time at Public Citizen's Health Research Group, a consumer advocacy organization founded by Ralph Nader in 1971. My comments today deal exclusively with the Concept Paper entitled *Risk Assessment of Observational Data: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment,* distributed by the FDA.

Drugs are approved and reach the market after testing on a relatively small number of patients and under rigorous scrutiny. Once on the market, the approved drugs may be given to patients with multiple disorders or even for unapproved indications. Unexpected adverse reactions may therefore occur, or expected reactions may occur at an increased rate. This argues for an effective postmarketing surveillance system.

The FDA has often asked the sponsoring drug companies to perform Phase 4 postmarketing studies of worrisome drugs, but the studies are frequently never completed, not published, or difficult to interpret due to design problems. The recent Health and Human Services Office of the Inspector General report *FDA's Drug Review Process for New Drug Applications: A Management Review* notes that Medical Officers are "often uncertain about what types of postmarketing commitments to request of sponsors." Consequently, we suggest that the FDA's Office of Pharmacoepidemiology and Statistical Science also be involved in the design of Phase 4 studies and other postmarketing programs.

The Health Research Group has documented the failure of drug companies to finish Phase 4 studies in a study we sent to then-Commissioner Jane Henney on April 13, 2000 (available at: http://www.citizen.org/publications/release.cfm?ID=6721). Five to ten years after making a Phase 4 commitment, only 13% of those commitments were completed. What does the FDA plan to do to correct this poor performance record by industry?

Recently, the postmarketing study for the asthma drug Serevent (the SMART study) was stopped by Glaxo because of excess deaths among the Serevent users, but the drug was left on the market and this important study is not available for inspection by the scientific community. This secrecy may serve the sponsors' needs, but it leaves physicians, scientists and patients in the dark. Another company (or even Glaxo itself) may now seek to market a drug with the same problems as Serevent, potentially costing more lives. Postmarketing studies that are not made public are, for all intents and purposes, postmarketing studies that never happened. (Conversely, were the SMART study to show some benefit for Serevent, we suspect there would have been a great rush to publish.)

We are also concerned that the promise of postmarketing studies may be used to approve new drugs inappropriately or delay the removal or relabeling of dangerous

drugs. In a survey of the FDA's reviewing Medical Officers that the Health Research Group conducted in 1998, many officers felt pressure to approve drugs that they might not have approved; the companies' promises of Phase 4 studies (many of which will presumably never be completed) tipped the balance for approval (available at: http://www.citizen.org/publications/release.cfm?ID=7104).

My next comment concerns the criteria for assessing causality in postmarketing studies. This section is brief and mentions criteria without assigning any priority or weight to each criterion. I think that is probably a wise policy as there are little data to support such a weighting or score. But the paper should be clearer with respect to the notion that these are ideal conditions for assessing causality. In particular, we would not want case reports that involve the use of drugs in addition to the suspect drug (line 335) to be summarily dismissed. The paper does not mention the many epidemiological and statistical techniques available to deal with confounding by the presence of other medical conditions or the use of other drugs.

The Concept Paper is also unnecessarily dismissive of reported rates of adverse drug reactions (line 284). While we agree that, wherever possible, reported numbers of cases should be adjusted for prescribing rates, prescribing data -- especially for narrow demographic groups -- are often lacking. Sometimes the "signal" of reported numbers of cases is so strong that it alone can suggest the need for FDA action. The current language applies too strong a standard and may lead to lack of FDA action when the protection of the public requires such action.

Finally, analysis by so-called "race" is listed (line 308) as important in assessing safety signals. We advocate extreme caution in invoking "racial" explanations for observed adverse reactions. This is because the "races" have far more genetic similarities than they have differences. If analysis by race is used, the racial categories must be listed, clearly defined and justified, and the rationale for the use of this variable detailed.

Thank you for your attention to my remarks.