Testimony of

Sharon Levine, M.D.

Associate Executive Director

The Permanente Medical Group, Inc.

on behalf of the

Kaiser Permanente Medical Care Program

Before the

Committee on Energy and Commerce
Subcommittee on Health
U.S. House of Representatives

May 9, 2007

Chairman Pallone, Congressman Deal, and distinguished Subcommittee members, I am Dr. Sharon Levine, a pediatrician and Associate Executive Director of The Permanente Medical Group (TPMG), which together with Kaiser Foundation Health Plan and Kaiser Foundation Hospitals make up Kaiser Permanente's Northern California Region. One of my responsibilities is to oversee our Medical Group's efforts on drug use management, and to partner closely with my Health Plan pharmacist colleagues in delivering high quality, safe and effective pharmaceutical services to our members. I appreciate the opportunity to testify here today on the important subject of prescription drug safety. No issue is more important to those of us intimately involved in providing medical and pharmaceutical care to Kaiser members than the safety of the drugs we prescribe and dispense.

I am testifying today on behalf of the national Kaiser Permanente Medical Care Program. Kaiser Permanente is the nation's largest integrated health care delivery system. We provide comprehensive health care services to more than 8.7 million members in our 8 regions, located in 9 states (California, Colorado, Georgia, Hawaii, Maryland, Ohio, Oregon, Virginia and Washington) and the District of Columbia. In each Region, the nonprofit Kaiser Foundation Health Plan enters into a mutually exclusive arrangement with an independent Permanente Medical Group to provide or arrange for all medical services required by Health Plan members.

In our organization, virtually all pharmacy services are provided directly in Kaiser Permanente facilities by Health Plan employed pharmacists. This year, the more than 15,000 Permanente physicians and their practitioner colleagues will prescribe or furnish over 65 million prescriptions and Kaiser pharmacists will dispense more than $3 billion worth of prescription drugs. Our physicians and pharmacists make their best efforts to ensure that our members receive the highest quality and most cost-effective pharmaceutical care possible based on the best and most current clinical evidence. This is supported by a strong culture of cooperation and collaboration between our medical groups and our pharmacy program.

An important and very valuable benefit of fully integrating pharmacy services in our health care delivery system is that we are able to capture detailed information about the drugs we prescribe and dispense and to match that information with other clinical and demographic data in our delivery system.

I would like to spend a few minutes discussing what this means in terms of the ability to learn more about the safety and effectiveness of specific prescription drugs and to enable our researchers (and others) to help protect all Americans from drugs that pose an unacceptable risk compared to the benefits they may provide.

All drugs are potentially "dangerous" and this is an important point for consumers to understand. Today, we are focused more narrowly on the fact that some drugs may be too dangerous considering the potential benefits they provide, and that we have not done enough to determine which drugs those are before there is aggressive marketing, rapid uptake and broad exposure to the drugs. We believe that carefully and systematically

examining data on drug use early in a drug's post-approval appearance in the market, we can better and more rapidly identify safety problems--hopefully before rapid uptake of drugs in the market exposes many people to associated risks.

For much of this testimony I owe a debt of gratitude to my colleagues Dr. Joe Selby, of Kaiser Permanente's Division of Research, and Drs. Michele Spence, Rita Hui and Jim Chan of our Pharmacy Outcomes Research Group, the talented health researchers currently using our databases to confirm or disprove suspected safety problems with specific prescription drugs. We are hoping to partner with colleagues at the FDA on several projects, and continue work on other drug safety issues of interest to Kaiser Permanente researchers and clinicians.

Drug Safety and the Use of Kaiser Permanente Databases

Background

New drugs continue to appear at an ever-increasing rate and a growing proportion of children and adults take medication regularly. There is a need to strengthen several aspects of the safety monitoring and evaluation process once drugs reach the market so that adverse effects of medications can be detected and quantified as early as possible.

Evaluation of drug safety in the U.S. has relied primarily on data from pre- (Phase I-III clinical trials for both safety and efficacy) and post-marketing clinical trials and on information collected from spontaneous reporting systems.[1, 2] While clinical trials will often detect common adverse events, they are unable to identify all side effects. The size of pre-marketing trials is such that adverse events as common as 1/1000 patients often go undetected before marketing.[3] Post-marketing trials are not routinely performed and, though larger, are still insensitive to less frequent but potentially severe adverse effects. Moreover, the selection of patients for both pre- and post-marketing trials usually eliminates individuals with coexisting diseases as well as the very old and very young. These groups may be most at risk for adverse effects. Thus, results may be poorly applicable to the full population that will eventually be exposed to the drug. Another important limitation of pre-marketing trials is that they are usually of short duration (i.e., months) and therefore likely to miss adverse effects that emerge only after prolonged exposure.

The current U.S. system for post-marketing monitoring of drug safety depends extensively on the voluntary reporting of adverse events by providers, consumers, and pharmaceutical companies. This system has several limitations. It is estimated that at most only 10% of adverse events are reported to the FDA.[4] In addition, the FDA cannot estimate the risk of these events as it does not also have information on the number of individuals receiving the drug (denominators). A particular weakness of spontaneous reporting systems is the inability to identify adverse effects that are common, but are modestly increased by use of the drug (e.g., a 2-fold increase in risk). Modest increases in common events have a much greater public health impact than very rare adverse events.[5]

Deficiencies in the current approach to monitoring drug safety in the U.S. have been highlighted in recent years by reports from both clinical trials and observational studies showing an increase in risk of coronary artery disease associated with the widely used Cox-2 inhibitors.[6-12] Although myocardial infarction is a relatively common event among adults in the U.S., the association with certain of the Cox-2 inhibitors was not firmly established until the drugs had been in widespread use for more than 5 years.

Large observational, epidemiologic studies of outcomes related to use of marketed drugs are often the best means of relatively quickly evaluating risk signals detected either in smaller clinical trials or by spontaneous reports, particularly when existing clinical databases can be used to conduct appropriate studies.

Essential ingredients for efficient and valid observational studies of drug safety include a very large population that is stable, in terms of remaining under observation; that is diverse, in terms of both socio-demographic characteristics and health status; and for which accurate, automated records are available for measuring drug exposure over time, for completely capturing the occurrence of endpoints (adverse events), and for measuring clinical characteristics that may confound observational comparisons. In such a setting, many appropriate studies can be completed as longitudinal or cohort analyses. In some instances, more primary data collection will be required to measure additional predictors that could differ between persons exposed to the drug of interest and those unexposed. Ready access is needed to all relevant medical records, and occasionally to the patient population (via interviews or surveys) or to prescribing physicians, in order to measure important covariates such as indications for the medication.

Kaiser Permanente Clinical Databases

Kaiser Permanente (KP) is an integrated, prepaid, group model health care delivery system that currently has nearly 6.4 million enrolled members in California. This membership is significantly more stable than that of most other large health plans or systems, with average member tenure of more than twelve years. KP's automated administrative and clinical databases are unparalleled in their detail and completeness and therefore offer important advantages--in addition to population size--for evaluating possible adverse effects of pharmaceuticals. Chief among these advantages are the availability of nearly complete laboratory test results, both inpatient and outpatient; detailed coded data on all outpatient diagnoses and procedures (as well as complete inpatient data); rapid access to paper medical records for past and present members; a uniform electronic medical record that is currently being implemented; extensive experience surveying members (patients) by mail, telephone, and internet; and the ability to successfully identify, survey and interview prescribing physicians. KP databases have been used in numerous published studies for many years; all databases are readily linked over time via a unique medical record number; most data are available within days of clinical transactions. Because these databases have been in operation since 1995, a large population has been under observation for at least a portion of the past decade.

Each of the data sources listed in Table 1 represents one single database in each of our Northern and Southern California Regions, with uniform data entry standards. Both pharmacy and laboratory databases are directly archived from online clinical systems and are thus complete and accurate. Because KP is comprehensive and fully integrated, no element of care (e.g., mental health, chemical dependency, or chronic disease management) is "carved out" and therefore unavailable to researchers. All databases are complete for 10 years or more and therefore allow study of longer term outcomes.

Table 1 Basic KP Databases

	Comments
Membership Data	Monthly updates of membership status for each member, along with demographics (age, sex, residential address and zip code).
Hospital Discharges	KP captures hospital discharges from its 25 California hospitals and claims from outside hospitals (10% of admissions); primary discharge diagnosis (ICD-9), secondary diagnoses; multiple procedures; DRGs, admission status (elective/non-elective; and discharge status.
Outpatient Rx Data	Captures all prescriptions and refills dispensed; data include NDC codes, therapeutic classes, quantity, strength, daily dosage.
Outpatient Dx Data	Multiple ICD-9 diagnostic codes per outpatient visit; both primary and specialty; CPT-4 procedure codes
Laboratory Data	Complete outpatient and inpatient laboratory data for all hospitalizations at KP hospitals, including test results

Membership data are updated on a monthly basis; and contain demographic information (age, sex, residential address, and social security number) that allows automated statistical adjustment or matching, and linkage to U.S. census socio-economic data and to mortality data. Both regions (North and South) have geographically coded all member data to 2000 U.S. census block group data to provide proxy measures of socioeconomic status. Member addresses are updated at every clinic visit by clinic staff, which helps us maintain a very high contact and response rate to telephone and mailed surveys of KP members. Self-reported race/ethnicity information is recorded for all hospital discharges (see below) and is captured in member surveys. Together, these sources provide race/ethnicity information for more than 60% of members, with higher proportions among women and older patients. With the arrival of the new electronic medical record in 2006-08 (discussed below), race/ethnicity data will be routinely captured by the Health Plan and confirmed at outpatient visits in each region. With this capability we will eventually approach 100% capture of this data which we believe is essential to resolving health disparity issues.

Hospital discharge data. Most hospital discharges (90%) for KP members come from one of 25 KP-owned hospitals in California. At these hospitals, diagnoses (up to 15) and procedures (up to 11) are entered by coders who have been centrally trained and who use the identical coding software. The remaining 10% of discharges come from non-KP hospitals and are captured in a claims database with similar data elements. Many discharge diagnoses have been validated using medical record reviews.

Prescription data. Both inpatient and outpatient prescription data from more than 180 KP pharmacies are captured for nearly 100% of enrollees in both systems.

Approximately 95% of KP members have a pharmacy benefit. Moreover, KP pharmacies are located in or near all of our medical office buildings where outpatient services are provided. Convenient online and telephone refills are also heavily used. Thus, there is little incentive for members to fill prescriptions elsewhere. A recent survey among members with diabetes confirmed that only 3.3% reported obtaining any prescription outside of KP during the previous year. The small proportions of members without a drug benefit are often excluded from studies involving ascertainment of drug exposures. Prescription data include NDC codes and standard drug class codes (allowing for rapid selection of all drugs/strengths/ preparations within major therapeutic classes, such as oral hypoglycemics). Prescription databases also capture dates of dispensing, strength, daily prescription, and number dispensed (for calculating days supply, exposure over time, and adherence). Historically, prescription systems have not captured medications administered in ambulatory clinical settings, such as infused chemotherapeutic agents. However, all facilities in both KP California regions are in the process of implementing the pharmacy component of the new electronic medical record which will capture all such clinic-administered medications routinely.

Outpatient diagnosis data. Complete outpatient diagnosis data capture is a major advantage of KP databases. Diagnoses (from one to many) are recorded by clinicians at every ambulatory visit using optically scanned, specialty-specific encounter forms. Diagnoses are coded using an adapted ICD-9-CM coding system. In addition to identifying specific endpoints that may represent adverse events, these diagnoses are useful for assessing co-morbid conditions, either singly or in combination. Outpatient diagnoses are not likely to be as accurate as hospital discharge diagnoses. However, chart review validations of several outpatient diagnoses have been reported. In KP Northern California's diabetes registry, outpatient diagnoses captured more than 97% of all diabetic patients identified from any source, and only 9% of those identified by outpatient diagnoses were not also identified from at least one other source. Thus, outpatient diagnoses for diabetes appear to be both sensitive and specific. The outpatient database also captures procedures performed (e.g., retinal exam, sigmoidoscopy, pap smears) and clinical measurements such as blood pressure levels, body mass index, and smoking status. On January 1, 2004, both recent blood pressure values and smoking status were available in more than 92% of adult members in Northern California. These latter variables are useful in adjusting for case-mix differences (confounding) and also for disease severity differences.

Laboratory testing and results. Most laboratory testing in each region is performed in a single centralized, very high volume regional laboratory. Urgent testing is performed at hospital medical centers, but these results are also fed into the same database which supports both the clinical electronic medical record and archived databases used for research and quality assurance.

Many other research databases have been created within KP from these basic datasets. These include many registries (e.g., cancer, diabetes, HIV/AIDS, and total joint replacement). Some of these databases exist in only one region, but the code used to create each registry can be applied to the source data from the other regions.

The advantages of having such rich clinical data lie primarily in the ability to create detailed definitions of specific adverse drug events from electronic data. For example, it is a simple step to combine a discharge diagnosis of myocardial infarction (MI) with lab results showing cardiac enzymes to confirm or characterize diagnoses of MI; toxic hepatitis with repeated liver function test results; or neutropenia with repeated measures of white blood cell counts. Similarly, allergic reactions can be linked to prescriptions for oral corticosteroids to select more severe reactions.

Paper medical records. The ability to rapidly retrieve paper medical records dating back for more than 10 years is a unique advantage of integrated systems such as KP. After review and approval by a KP IRB, researchers may access these records for review. Research center staff work closely with medical records staff in KP facilities to retrieve both outpatient and inpatient records in full compliance with HIPAA requirements.

Fully computerized inpatient and outpatient medical record. KP is midway through the implementation of an entirely computerized inpatient and outpatient medical record, called "HealthConnect" across our entire program. (HealthConnect is the KP name for an Epic Systems electronic medical record.) Implementation has been completed in several of KP's smaller regions, is well underway in KP Southern California and has begun in Northern California. The pharmacy component is completed and it is anticipated that the entire record will be in full use throughout both regions by the end of 2008. This record includes prescription order entry in both inpatient and outpatient settings. It includes full text notes which can be scanned using text-processing to enhance the sensitivity and possibly the specificity of potential adverse events. The new record will routinely record self-reported race/ethnicity, as well as all vital signs. It will replace the need to retrieve paper records and allow analysts to simply scan records on screen for information that is not coded and archived in searchable databases.

Examples of Drug Safety Studies using KP Databases

Most of the recent studies that we have conducted have taken place within four separate research units that operate within the KP Northern and Southern California regions. These research units include the Division of Research (DOR), KP Northern California; the Research and Evaluation Department (R&E), KP Southern California; and Pharmacy Analytic Services (PAS) and Pharmacy Outcomes Research Group (PORG), both of which serve all of California. In the past two years, these four groups have combined to form the Kaiser Permanente California Pharmacoepidemiology Group (KPCPG). The KPCPG is a collaborative of KP researchers who have extensive experience conducting pharmacoepidemiologic studies, and a strong interest in collaboration with the FDA on studying possible adverse effects of FDA approved medications in the market, and experience collaborating with one another on a variety of studies. Following are several examples of important studies that we have conducted or will soon start using the resources I have described above.

1. Statin Use and rhabdomyolysis (muscle damage). In 2002, KP undertook a large-scale transition in statin use. Using a system-level intervention, more than 35,000 KP California members switched from other statin agents to lovastatin. By the end of the

transition, 80% of all statin users were on lovastatin (compared with 50% pre-intervention). Prior to the transition, KP clinicians had raised concerns regarding possible increases in rhabdomyolysis as a result. Researchers in PORG conducted a prevalence study over a one year period to identify the frequency with which elevations of serum creatine kinase (CK) were noted in persons taking a statin drug and to estimate the relative prevalence by statin preparation and dosage.[13] Lovastatin, even in high doses, was not associated with an increased risk of high elevations of CK compared with a moderate to high dose of simvastatin. Other clinical characteristics were also examined as possible predictors of high elevations of CK. Additional significant predictors of a high elevation of CK included elevated serum creatinine; use of a potentially interacting medication; male gender; and diabetes. The ability to go beyond simple detection of associations of drugs with adverse events to identify additional clinical characteristics that predispose some recipients to experience the adverse event given the exposure is a benefit of the very large size of our population and the richness of the automated clinical data.

2. Rofecoxib and the risk of acute myocardial infarction and sudden cardiac death. Concern that rofecoxib may increase the risk for serious cardiovascular events was first raised in a post-marketing clinical trial of its relative effectiveness.[9] Members of PORG, in collaboration with FDA, conducted a large case-control study nested in a cohort of over 1.3 million users of COX-2 selective and non-selective nonsteroidal anti-inflammatory agents. They found that rofecoxib increases the risk of serious coronary heart disease. This study, together with data from another clinical trial using rofecoxib to prevent colorectal adenomas, led to withdrawal of the agent by its manufacturer in October 2004.[11,12]

3. Topical tacrolimus/pimecrolimus and the risk of cancer. In March 2005 FDA issued an advisory to doctors urging caution in prescribing topical tacrolimus or pimecrolimus because of an increased risk of cancer. The concern was based solely on information from animal studies, case reports in a small number of patients and the pharmacology of the drugs. At KP, we have the capability of merging our pharmacy database with our cancer registry thus identifying patients who have been prescribed these two drugs and diagnosed with cancer. PORG compared the rate of different cancers among patients with eczema or atopic dermatitis who have or have not been exposed to topical tacrolimus or pimecrolimus. The preliminary result of the study included close to 1 million California members with 2.5 million person-years of follow up time. KP researchers did not find an increase in overall cancer rates but there was an increase in cutaneous T cell lymphoma among drug users. Since KP is integrated, our researchers were able to examine the electronic and paper medical records of some of these cases of cutaneous T cell lymphoma. These allowed us to confirm these cases and exclude those that the physicians suspected of having cancer prior to receiving the drugs. KP researchers concluded that there was no increased risk of cancers or T cell lymphoma following exposure to either topical tacrolimus or topical pimecrolimus.

4. Attention-Deficit/Hyperactivity Disorder (ADHD) medications and the risk of serious cardiovascular disease. Funded by the FDA, this study is currently underway and is a collaborative effort involving KPCPG, Vanderbilt University, United HealthCare, and the HMO Research Network. According to a summary from the FDA's Adverse Events Reporting System; cardiac arrest, myocardial infarction, and death are among the top 50 most commonly reported adverse events for ADHD medications. Of all deaths, a substantial number were cardiac deaths, associated

either with sudden collapse or with symptoms of MI. Deaths were reported in both children and adults. This retrospective cohort study will analyze whether these medications confer an increased risk for cardiovascular disease in children and adults.

5. Aromatase inhibitors and the risk of hip fracture among breast cancer survivors. In 2004, the American Society for Clinical Oncology recommended aromatase inhibitors as a first line adjuvant therapy for postmenopausal, hormone receptor-positive breast cancer. The Society noted, however, that the long-term consequences of aromatase inhibitor therapy, specifically osteoporosis, are not well characterized. Clinical trial results suggest that an increased frequency of hip fractures accompanies aromatase inhibitor use in the prevention of breast cancer recurrence. However, this association has not been quantified in a large population of breast cancer survivors that is representative of all women treated in clinical settings. Rather it has been limited to women eligible and willing to participate in a treatment trial. The goal of this study, conducted by PORG in collaboration with researchers from Wake Forest Medical Center and the University of Michigan, is to estimate the risk of hip fracture hospitalization among approximately 9,000 KP breast cancer survivors receiving aromatase inhibitors (anastrozole, letrozole, exemestane) compared to those receiving tamoxifen therapy.

6. Atypical Antipsychotics and onset of diabetes. Another safety study in the planning stage is to assess the incidence and comparative rates of newly diagnosed diabetes and other indicators of metabolic syndrome in patients receiving different atypical antipsychotic agents. The use of atypical antipsychotic drugs has been associated with the development of a metabolic syndrome, whose core features include insulin resistance, type 2 diabetes, dyslipidemia, hypertension, and abdominal obesity. The integrated KP databases--including over 6 million enrolled members, full laboratory results and detailed coded data on outpatient diagnoses--is the ideal setting for this study. KP researchers will assess the relative risk of drug-induced new onset diabetes as differential effects on plasma lipids such as LDL-cholesterol, HDL-cholesterol and triglycerides. Results from this study will provide clinicians with added information to help guide their choices of atypical antipsychotics for individual patients

Concluding Remarks

These are just a few examples of what is possible in terms of using existing data, and the future availability of complete clinical data capture with electronic medical record systems like Kaiser Permanente's HealthConnect, to enhance significantly the ability of researchers to more quickly identify problems. The experiences we are gathering today will help shape our ability to take full advantage of the new digital health care environment, to improve the safety of drug therapy and to understand more fully the risk-benefit profile that specific drugs offer to individual patients.

If we are to take full advantage of this research capability to substantially increase the safety of prescription drug use in this country we need *time* to find safety problems before too many people are exposed to unproven new drugs. The aggressive marketing of new drugs both before and after FDA approval--including drugs that are only marginal improvements over existing therapies--does not allow sufficient time for this to happen. A solid case can be made for policies that would make drugs available in a more well-organized and thoughtful manner. Certainly this

committee will have a great deal to say about that, and I encourage you to explore ways to make sure that drugs not only come to market in a timely manner, but also that the data collection that follows release and marketing is organized in a manner that avoids exposing patients to unnecessary risk.

We would also ask that you consider making additional resources available to the FDA and to the research community to pursue answers to questions raised about particular drugs and conduct broad post-market surveillance activities.

Finally, I hope that it is clear from my testimony that the expanded use of comprehensive, clinically based electronic health records is vital to improving our research capabilities. It will be essential that the public and private sectors cooperate to ensure that the appropriate data elements are widely used and the ability to match appropriate clinical, demographic, encounter and related data elements across providers is built in to these systems.

Thank you again for the opportunity to testify today. I look forward to your questions.

References

1. Kennedy DL, Goldman SA, Lillie RB. Spontaneous reporting in the United States. In: Strom BL (ed). Pharmacoepidemiology, 3rd edition. New York: John Wiley & Sons, 2000:151-74.
2. Kessler DA. Introducing MEDWatch: A new approach to reporting medication and device adverse effects and product problems. JAMA. 1993; 269:2765-2768.
3. Nies A, Spielberg S. 1996. Principles of therapeutics. *In* Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG (eds): Goodman and Gilman's the Pharmacological Basis of Therapeutics. New York, McGraw-Hill, pp. 43-62.
4. Brewer T, Colditz GA. Postmarketing surveillance and adverse drug reactions: current perspectives and future needs. JAMA 1999;281:824-29.
5. Kaufman DW, Shapiro S. Epidemiological assessment of drug-induced disease. Lancet. 2000;356:1339-43.
6. Fontanarosa PB, Rennie D, DeAngelis CD. Postmarketing surveillance--lack of vigilance, lack of trust. JAMA 2004;292:2647-50.
7. Topol EJ. Failing the public health--rofecoxib, Merck, and the FDA. N Engl J Med 2004;351:1707-9.
8. Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, Makuch R, Eisen G, Agrawal NM, Stenson WF, Burr AM, Zhao WW, Kent JD, Lefkowith JB,Verburg KM, Geis GS. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. JAMA 2000; 284:1247-55.
9. Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, Day R, Ferraz MB, Hawkey CJ, Hochberg MC, Kvien TK, Schnitzer TJ; VIGOR Study Group. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. N Engl J Med 2000; 343:1520-8.
10. Solomon SD, McMurray JJV, Pfeffer MA, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. NEJM. 2005; 352(11):1071-1080.
11. Bresalier RS, Sandler RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. NEJM. 2005; 352(11):1092-1102.
12. Graham DJ, Campen D, Hui R, Spence M, Cheetham C, Levy G, Shoor S, Ray WA. Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study. Lancet. 2005;365:475-81.
13. Chan J, Hui R, Levin E. Differention association between statin exposure and elevated levels of creatinine kinase. Annals of pharmacotherapy 2005; 39:1611-1616.

*Summarized from an RFP submitted to FDA for post-marketing pharmacosurveillance written by Dr. Joe Selby on behalf of KPCPG.