Statement of Alexander M. Walker, MD DrPH
February 25, 2008

Qualifications

I have conducted studies on the safety of drugs, vaccines and medical devices throughout my career, and as a result the conduct and interpretation of such research is an area of my professional expertise.

My resume, with a publication list, is attached to this statement. In brief, I have received degrees in biochemistry (AB 1970), medicine (MD 1974) and public health (DrPH 1981) from Harvard University. I joined the faculty of the Harvard School of Public Health in 1980 as an Assistant Professor. When I left Harvard to join Ingenix in 2000, I was Professor of Epidemiology and Chair of the Department of Epidemiology. At Ingenix, I directed numerous studies of the safety of pharmaceutical products, including research on the ORTHO EVRA™ transdermal contraceptive system, which I will refer to in this document as the "patch." I left Ingenix in 2007 to found a consulting and research firm and to dedicate more time to my teaching at Harvard, where I am an Adjunct Professor of Epidemiology.

World Health Information Science Consultants, LLC, is being paid $500 per hour for my services.

I have not testified by deposition or by appearance in court in the last four years.

Reports reviewed in preparation of this statement

I have reviewed work undertaken by our group at i3 Drug Safety (an operating unit of Ingenix), which was published in 2006, as well as an *ad hoc* study that we carried out in 2006.[1,2] I have reviewed the published reports of studies undertaken by Dr. Hershel Jick

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[1] Cole JA, Norman H, Doherty M, Walker AM. Venous thromboembolism, myocardial infarction, and stroke among transdermal contraceptive system users Obstet Gynecol 2007;109:339-346. *Cole 2007.*

[2] i3 Drug Safety. The Risk of Venous Thromboembolism, Myocardial Infarction, and Ischemic Stroke Among Women Using the Transdermal Contraceptive System Compared to Women Using Norgestimate-Containing Oral Contraceptives With 35 mcg Ethinyl Estradiol Analysis of Claims-Based Venous Thromboembolism Case Definition. Final Report. June 30, 2006. *i3 Drug Safety 2006.*

and his collaborators at the Boston Collaborative Drug Surveillance Program (BCDSP).[3, 4, 5, 6, 7] Additionally, I have been provided with and consulted more extensive unpublished BCDSP reports of the same studies.[8, 9, 10, 11, 12] I have reviewed a summary

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[3] Jick SS, Kaye JA, Russmann S, Jick H. Risk of nonfatal venous thromboembolism in women using a contraceptive transdermal patch and oral contraceptives containing norgestimate and 35 mcg of ethinyl estradiol. Contraception. 2006 Mar;73(3):223-8. *Jick 2006a.*

[4] Jick SS, Kaye JA, Russmann S, Jick H. Risk of nonfatal venous thromboembolism with oral contraceptives containing norgestimate or desogestrel compared with oral contraceptives containing levonorgestrel. Contraception. 2006 Jun;73(6):566-70. *Jick 2006b.*

[5] Jick SS, Jick H. Cerebral venous sinus thrombosis in users of four hormonal contraceptives: levonorgestrel-containing oral contraceptives, norgestimate-containing oral contraceptives, desogestrel-containing oral contraceptives and the contraceptive patch. Contraception. 2006 Oct;74(4):290-2. *Jick 2006c.*

[6] Jick S, Kaye JA, Li L, Jick H. Further results on the risk of nonfatal venous thromboembolism in users of the contraceptive transdermal patch compared to users of oral contraceptives containing norgestimate and 35 microg of ethinyl estradiol. Contraception. 2007 Jul;76(1):4-7. *Jick 2007b.*

[7] Jick SS, Jick H. The contraceptive patch in relation to ischemic stroke and acute myocardial infarction. Pharmacotherapy. 2007 Feb;27(2):218-20. *Jick 2007c*

[8] Final Report, Postmarketing Study of ORTHO EVRA™ in Relation to Non-Fatal Venous Thromboembolism, Boston Collaborative Drug Surveillance Program, September 21, 2005

[9] Final Report of the 2006 Update on Postmarketing Study of ORTHO EVRA in Relation to Non-Fatal Venous Thromboembolism, BCDSP, January 16, 2007. *Jick 2007a.*

[10] Final Report, Postmarketing Study of ORTHO EVRA™ in Relation to Ischemic Stroke, Acute Myocardial Infarction and Cerebral Sinus Thrombosis, Boston Collaborative Drug Surveillance Program, December 15, 2005

[11] Report on the Comparison of the Risk of Diagnosed Nonfatal VTE Comparing Women Who Were Current Users of Norgestimate-Containing Oral Contraceptives or Desogestrel-Containing Oral Contraceptives with Current Users of Levonorgestrel-Containing Oral Contraceptives, Boston Collaborative Drug Surveillance Program, December 18, 2005. *Jick 2005.*

[12] Report, Postmarketing Study of ORTHO EVRA™ and Levonorgestrel Oral Contraceptives Containing Oral Contraceptives with 30 mcg of EE in Relation to Non-

discussion of the differences between i3 Drug Safety and BCDSP studies by Prof. Noel Weiss.[13]

The Studies

All of the research on the comparative safety of the patch and oral contraceptives has been conducted as case-control studies "nested" within the cohort information derived from large insurance databases. This kind of epidemiologic study is standard in drug safety research, and represents the fastest and most efficient way to obtain information concerning relatively infrequent health events among people who receive widely used pharmaceuticals.

An epidemiologic cohort consists of individuals followed for some relevant period of their lives. Health events are ascertained and related to characteristics of the individuals. The amount of exposure to contraceptives in these studies was quantified in terms of "woman-years." A woman-year is a summary measure corresponding to the experience of a hypothetical woman using contraception continually for one year. The occurrence of health events is presented as a rate, which is calculated as the number of events divided by the number of woman-years. A nested case-control study within the cohort compares cases to women selected from the cohort in such a way as to permit detailed examination of the patterns of use of contraceptives and other factors as they might relate to case occurrence.

These studies are efficient when carried out inside large administrative schemes such as health insurance plans, where the insurance claims provide information on contraceptive use and health events for hundreds of thousands of women. Such studies provide data on the health effects of drugs on more people than could possibly be included in a randomized clinical trial or a prospective registry of drug users. The nested design means control groups can be selected quickly and with assurance that the individuals properly represent the contraceptive users whom one wishes to study.

i3 Drug Safety Study – Cole et al. 2007

J. Alexander Cole and our colleagues at i3 Drug Safety undertook a case-control study that was nested within a cohort of women who used either the patch or a combination oral contraceptive (COC) containing the synthetic progestational agent norgestimate. When a woman takes a COC containing norgestimate, her liver metabolizes the norgestimate to norelgestromin, which is the synthetic progestin contained in the patch. Thus women using the patch and women taking a COC-norgestimate pill are exposed to similar hormones, but differ in the mode by which the hormones have been taken in.

Fatal Venous Thromboembolism, Ischemic Stroke and Myocardial Infarction, June 15, 2007. *Jick 2007c.*

[13] Email identified as "From: Noel S. Weiss [mailto:nweiss@u.washington.edu] / Sent: Sunday February 12, 2006 3:51 PM / To: Mohan, Aparna [BRMUS] / Subject: EVRA"

The i3 Drug Safety cohort consisted of users of the patch or the norgestimate COC who were receiving health insurance through UnitedHealthcare, a large US health insurance company. Follow-up began with the first dispensing of one of these contraceptives after April 2002 and continued through December 2004, or until a woman stopped using the contraceptive or left the health insurance plan, if one of those events came earlier. Cole and his coworkers identified cases of venous thromboembolism (VTE) by searching all health insurance claims, examining the chronological sequence of claims to rule out plainly spurious codes, and then reviewing the medical record to identify cases that met predetermined confirmation criteria.

There were just under 50,000 woman-years of patch use and just over 200,000 woman-years of COC-norgestimate use. There were 20 cases of VTE in the patch cohort and 37 in the COC-norgestimate cohort. Direct calculation of the rate of VTE gave 40.8 cases per 100,000 woman-years in patch users and 18.3 cases per 100,000 woman years for the COC-norgestimate users. The ratio of these two rates is 2.2, and statistical evaluation yields 95% confidence limits of 1.3 and 3.8. (Confidence limits account for the fact that any study that is not infinitely large is subject to the effects of chance fluctuations in diseases rates. 95% confidence limits denote the possible true values of the rate ratio with which these data might be compatible, according to a standard statistical test.)

The nested case-control study involved comparing the cases to women selected at random from the cohorts with matching on age, calendar time and whether the current contraception followed on a prior course of hormonal contraception. In the nested case-control study, i3 Drug Safety was also able to restrict attention to women who did not have immediate precipitating factors such as trauma or surgery. The case-control analysis yielded a rate ratio estimate of 2.0, with 95% confidence limits of 1.0 and 4.1. Among women without immediate precipitating factors the rate ratio estimate was 2.4, with 95% confidence limits of 1.1 and 5.5.

The data available to i3 Drug Safety were statistically consistent with a wide range of possible elevated risks of VTE in patch users as compared to users of COC-norgestimate, from just detectable to as much as a five-and-a-half fold increase, and the similarity of the maximum likelihood "point estimates" (2.2, 2.0, 2.4) indicates that the various possible biases corrected by different analyses had no substantial impact on the outcome.

Cole and his colleagues examined the occurrence of acute myocardial infarction (AMI) and thrombotic stroke in the same cohorts of users of patch and COC-norgestimate, using the same technique as for VTE. For AMI and stroke, the number of cases of each of these conditions was ten, as compared to the 57 total cases in the VTE analysis. Ten cases split between two groups is such a small number that statistical fluctuations will obscure almost any possible medical interpretation of the findings. The numbers of AMI were three and seven, respectively, in patch and COC-norgestimate users, and the numbers of strokes were zero and ten, respectively. In the light of the woman-years of the cohort (50,000 patch and 200,000 COC-norgestimate), the statistically expected distribution of 10 cases would have been two in patch users and eight in COC-

norgestimate user. AMI cases in patch group were in slight excess (one extra case), and the stroke cases were in deficit (two cases fewer than expected). Because of the small numbers involved, neither of these comparisons should be taken as determinative evidence of a difference in risk between patch users and users of COC-norgestimate.

BCDSP Studies

In two studies that encompassed the period from April 2002 through September 2006, The Boston Collaborative Drug Surveillance program reviewed insurance claims data aggregated by PharMetrics, a company that provides benchmarking and analytic services to some 80 small and intermediate sized health plans across the United States. Available data include all paid claims for medical services, drugs and facility costs, linked by common, coded patient identifiers. The large health plan in which i3 Drug Safety studies were conducted is not included in the PharMetrics database.

BCDSP conducted case-control studies of VTE in PharMetrics data that were very similar in design to the nested study conduct by i3 Drug Safety in UnitedHealthcare data. Both databases represent persons with commercial health insurance across much of the United States. The principal differences were: (1) the BCDSP studies involved case confirmation only through review of the insurance claims data whereas the i3 Drug Safety study depended on a review of the underlying medical record; (2) the BCDSP studies required first-time use of COC-norgestimate after April 2002 in the COC-norgestimate cohort, whereas the i3 Drug Safety study permitted earlier use of norgestimate. Other differences were that the BCDSP did not check medical records for confounding factors and that the BCDSP did not include cases of fatal VTE.

Over the two studies, the BCDSP researchers found 51 cases of VTE among patch users (Jick 2006a: 31 users; Jick 2007b: 29) and 73 cases of VTE among COC-norgestimate users and (Jick 2006a: 37 cases; Jick 2007b 36 cases). Overall the estimated rate ratio from the two BCDSP studies was 1.0, with 95% confidence limits of 0.7 and 1.5. The reported incidence rates were 53 per 100,000 woman-years in patch users and 42 per 100,000 woman-years in norgestimate users.

Examining data through March 2005, the BCDSP found 18 cases of stroke in women who were currently using either the patch (eight cases) or COC-norgestimate (ten cases), and estimated the incidence rates at 14 and 11 per 100,000 woman years for patch and COC-norgestimate users, respectively. They found eight women with AME (one patch, seven COC-norgestimate) and estimated the incidence rates at 2 and 8 cases per 100,000 woman years for patch and COC-norgestimate users, respectively. (Jick 2007c)

In June 2007 the BCDSP submitted a report to Johnson & Johnson of a study conducted at the request of the European Medicines Evaluation Agency (Jick 2007c). The design was similar to that of the previous studies, except that users of the patch were compared to users of COCs containing a levonorgestrel, a different synthetic progestin. The numbers of patch versus COC-levonorgestrel exposed cases were 49 and 26, as opposed to sample control women's counts of 190 and 175, which after statistical analysis yielded

a rate ratio estimate 1.9, with 95% confidence limits of 1.1 and 3.3). The researchers reported 42,787 woman-years of patch use and 28,445 woman-years of COC-levonorgestrel use.

Comment

Lack of case confirmation may have biased the BCDSP results toward no-effect, but only modestly. The BCDSP researchers did not use medical records to confirm diagnoses of VTE in their studies. My collaborators at i3 Drug Safety and I pointed out that there was a relatively small proportion of cases of deep vein thrombosis among all VTE reported by the BCDSP, and that this suggested that the mildest forms VTE might have been selectively missed. Having heard this criticism, Johnson & Johnson sponsored an *ad hoc* study in which we applied the BCDSP's rule for adjudicating the insurance claims chronologies to our own insurance claims data, and found that it performed well. (*i3 Drug Safety 2006)* Essentially the BCDSP had looked for a diagnosis consistent with VTE on an insurance claims form, a charge for the performance of a diagnostic procedure, and the subsequent initiation of anticoagulant medication, which is the standard therapy for VTE. The BCDSP algorithm also called for removal from the VTE pool of cases who were later restarted on hormonal contraception. Applied to our data, where we had both insurance claims and the results of the chart reviews, the BCDSP algorithm captured 85 percent of the chart confirmed cases (this measure is called "sensitivity"). Of the cases identified by the algorithm as VTE 91 percent were confirmed in chart review. (That is, the "predictive value" was 91 percent.) These are excellent results, and it is unlikely that the case confirmation technique has played an important role in the differences between the studies. For a true rate ratio of 2.0, a predictive value of 91 percent would yield only about a five percent downward bias in the rate ratio estimate. Even if the predictive value were on the order of only 70 percent, the downward bias would be only about 20 percent.

Prior norgestimate use was not a distortive factor. The BCDSP researchers and we have commented on the differences in our original study designs, in which we admitted as COC-norgestimate users individuals who had used norgestimate before April 2002 and the BCDSP omitted them from the COC-norgestimate cohort. Both groups admitted women who had previously used COC-norgestimate into the patch user-cohort. Arguments on both sides stem from the decrease in risk with VTE over continued use of a hormonal contraceptive, which has been observed in past studies. We maintained that the BCDSP's omission of previously norgestimate-exposed women from the norgestimate-initiator group, together with their inclusion in the patch group meant that the patch users in the BCDSP studies were "survivors" of that particular progestational agent at the beginning of therapy with the patch, whereas the COC-norgestimate initiators were freshly exposed. The survivors of previous therapy, we argued, had effectively had at-risk women screened out, artificially depressing the incidence in the patch-using group. The BCDSP countered that our inclusion of individuals who had not newly initiated norgestimate use after April 2004 had artificially depressed the risk in the COC-norgestimate group. Each of these arguments has force only to the extent that large

proportions of the cohorts were in fact previous users of norgestimate. The proportion of cases and controls with early norgestimate use turned out to be small in our i3 studies. The i3 results were not changed when duration of use was brought into the analysis. Because members of the PharMetrics cohort were individuals in the same time and place as members of the i3 cohort, with similar kinds of health insurance, it is very likely that the patterns of drug use were similar between the cohorts. This source of bias therefore cannot have been large in either study, and cannot account for discrepancies between the results of the studies.

Statistical uncertainty was large. Even when studies are carried out to the highest technical standards, the point estimates that are commonly quoted in summarizing research tell the whole story only when the studies themselves are infinitely large. In the world of real-life research, we have to look to the confidence intervals to summarize the effects of statistical imprecision. Although they drew on large databases, the i3 Drug Safety and BCDSP studies admitted the possibility of substantial statistical noise, or chance effects, in their estimates. As noted before, the lowest 95% confidence bound of the i3 estimates was essentially at the no-effect level, whereas the highest yielded a rate ratio of 5.5 for the effect of the patch on the rate of VTE in comparison to the effect of COC-norgestimate. The combined patch *versus* COC-norgestimate rate ratio estimates from the BCDSP had a lower confidence bound of 0.7 and the upper bound of the patch *versus* COC-desogestrel comparison was 3.3.

Conclusion

In summarizing his review of the i3 Drug Safety and first BCDSP studies, Prof. Noel Weiss of the University of Washington said that "... the differences regarding VTE are NOT likely to lie in the differences in approaches to case definition or to differences in the sampling frame of the [COC-noregestimate] users. To me the leading candidate for the disparate VTE results is chance." (*Weiss 2006*) I agree.

I believe that the degree of elevation in the incidence of VTE associated with use of the patch *versus* other currently used COCs is likely to be somewhat above the region of complete overlap of the different confidence bounds drawn from the BCDSP and i3 Drug Safety studies. The true rate ratio is probably between 1.5 and 2.0. These rate ratios correspond to very small attributable risks, on the order of one to two cases per ten thousand women per year of patch use. This is similar to the level of comparative risk attributable to other widely used COCs, such as those containing for example desogestrel or gestodene.[14, 15]

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[14] Walker AM. Newer oral contraceptives and the risk of venous thromboembolism. (Review) Contraception 1998;57:169-181

[15] Hennessy S, Berlin JA, Kinman JL, Margolis DJ, Marcus SM, Strom BL. Risk of venous thromboembolism from oral contraeptivews containing gestodene and desogestrel. Contraception 2001 Aug;64(2):125-133

The small numbers of cases of AMI and stroke in the available data do not permit any strong conclusions, but taken overall they do not seem to point to difference in risk between users of the patch and COCs containing norgestimate.

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