

CONFIDENTIAL

BIOLOGICAL CLINICAL SAFETY AND PHARMACOVIGILANCE

***TWINRIX*[™] PREGNANCY REGISTRY PROTOCOL**

PPD [REDACTED], M.D., M.S.C.E.

11 May 2001

TABLE OF CONTENTS

	PAGE
1. SUMMARY	3
2. INTRODUCTION	4
3. METHODS	4
3.1. Registration and Follow-up.....	4
3.2. Inclusion criteria	5
3.3. Classification of Outcomes.....	5
3.4. Exclusions.....	6
3.5. Analysis	6
3.6. Timing of Reviews.....	7
3.7. Potential Biases	7
4. REFERENCES	9

1. SUMMARY

Although there is no evidence of teratogenicity from reproductive toxicology studies of Twinrix, GlaxoSmithKline (GSK) will manage this registry as part of an ongoing program of safety monitoring. Women judged to be at risk of hepatitis A and hepatitis B may be exposed to Twinrix before or during pregnancy. This registry is considered essential because of the potential for exposure during pregnancy and the unknown risks to pregnancy of any new chemical entity.

The purpose of the registry is to detect potential evidence of teratogenicity associated with prenatal use of Twinrix, if such teratogenicity exists, by collecting and analyzing voluntary (spontaneous), prospective reports of Twinrix prenatal exposures. Twinrix is designated as FDA Pregnancy Category C, which means that its safety in human pregnancy has not been determined. Registry statistics can supplement animal reproductive toxicology studies and assist clinicians in evaluating the potential risks and benefits of vaccination for individual patients. Registries do not collect control data from a comparison group, but proportions of birth defects in Twinrix-exposed pregnancies could be compared to the proportions of birth defects reported in the medical literature. A major limitation of an exposure-registration study is that the pregnancies that are reported may not be representative of all vaccinated pregnancies. Because reports of exposure are voluntary, they are subject to multiple biases.

Each registry report will contain a description of all prenatal exposures to Twinrix that are reported to GSK. Greater emphasis is placed upon pregnancies which are prospectively reported. Prospectively reported exposures are those reported while the pregnancy is ongoing; i.e., before the outcome is known. Because the outcome of the pregnancy is unknown when the prenatal exposure is reported, follow-up to determine the pregnancy outcome is required. Prospective reporting of ongoing pregnancies prior to knowledge of the pregnancy outcome reduces bias and permits estimation of the risk of birth defects.

The risk of pregnancy loss (also called miscarriage, spontaneous abortion, and intra-uterine fetal demise) is high early in gestation and decreases substantially from week 8 to week 28, yielding a cumulative estimated risk of 10-22% [Anderson, 2000, Fenster, 1997, Khattak, 1999, Osborn, 2000, Ventura, 2000, Wilcox, 1981, Wilcox, 1983, Wilcox, 1988, and Windham, 1997]. Although GSK will carefully review each pregnancy outcome, calculation of risk of spontaneous abortion should not be attempted and cannot be compared to background risk because pregnancies in this registry are reported at variable and, occasionally, imprecise times. Furthermore, pregnancy losses occurring early in gestation may not be recognized and/or reported. For example, if a pregnancy were recognized at 10 weeks of gestation and reported to the Registry, only a spontaneous abortion that was reported to the registry after this time would be available for analysis.

Retrospective reports, in which the pregnancy outcomes are known at the time of reporting, will also be reviewed. Retrospective reports are likely to be biased toward the reporting of more unusual and unfavorable outcomes and are less likely to be representative of the general population [Mitchell, 1988 and Wilcox 1984]. Therefore, the inclusion of such reports for calculation of probability (risk) of birth defects is

inappropriate. The purpose of summarizing the retrospective reports is to assist in the detection of any unusual patterns that may exist among the reported birth defects.

2. INTRODUCTION

The purpose of this Registry is to detect any major teratogenic effect in pregnancies intentionally or unintentionally exposed to Twinrix. The combination of the large number of women who are of reproductive capacity and live in hepatitis A- and hepatitis B-endemic areas, and the lack of data concerning exposure to Twinrix during pregnancy makes such a Registry an important component of the ongoing program to assess the safety of Twinrix. This is a prospective, voluntary, observational, exposure-registration study. Patient confidentiality will be strictly maintained. The purpose of the Registry is to prospectively collect data describing exposure to Twinrix before or during pregnancy, potential confounding factors (such as exposure to other medications), and information related to the outcome of the pregnancy. The Registry is intended to provide an early signal of potential risks in advance of results from formal epidemiologic studies. Registry data are used to supplement animal toxicology studies and to assist clinicians in weighing the potential risks and benefits of treatment for individual patients.

The Twinrix Pregnancy Registry will be maintained by Biological Clinical Safety and Pharmacovigilance. Enrollment in the Registry will begin at the time of commercial launch of Twinrix in the US. At the time of initiation of the Registry, pre-existing reports of pregnancy from clinical trials will be evaluated and enrolled when the criteria for registration are met.

3. METHODS

3.1. Registration and Follow-up

Reporting of exposed pregnancies is voluntary. Pregnancies will be registered following maternal exposure to Twinrix within 28 days prior to conception or during pregnancy. Registration of pregnancies is prospective, i.e., reported during pregnancy before the pregnancy outcome is known. Retrospective reports, i.e., those for which the outcome is known at the time of registration, will also be reviewed. However, because retrospective reports are more likely to be biased by relatively more frequent reporting of abnormal outcomes, such reports are less likely to be representative of the general population experience and, therefore, cannot be used for risk assessment or analysis [Mitchell, 1988 and Wilcox, 1984]. Health care providers with patients exposed to Twinrix during pregnancy will be encouraged to enroll their patients in the Registry as early in the pregnancy as possible to maximize the validity of the study. Health care providers can enrol their patients by calling the telephone number PPD [REDACTED].

When the pregnancy is reported prospectively, the Registry will collect registration data from the reporter through telephone interview or a short registration form. In the

CONFIDENTIAL

month of the estimated date of delivery follow-up will be sought by telephone contact or a form mailed to the health professional. Information about maternal events throughout the pregnancy, pregnancy outcome, and neonatal health is requested. Additional follow-up is not sought from subsequent health care providers.

A report of an exposure will be closed when clear information is received about exposure to Twinrix and pregnancy outcome determination, or when the patient is lost to follow-up. A patient is considered to be lost to follow-up when the Registry does not receive the minimum information, or if the reporting health care provider can no longer locate the patient. Only data from “closed” reports of exposed pregnancies with known outcomes will be considered for analysis.

3.2. Inclusion criteria

For a pregnancy report to be considered eligible for registration, certain data must be available. The required data include:

- Documentation that Twinrix was administered \leq 28 days before or during pregnancy;
- Confirmation that the pregnancy is being prospectively reported;
- Report made by a patient or a health care professional;
- The timing of the prenatal exposure to Twinrix (no broader than during which trimester);
- A patient identifier that will allow follow-up to be obtained so that the pregnancy outcome can be ascertained;
- Whether the patient was involved in a clinical trial at the time of the exposure;
- Full reporter contact information.

3.3. Classification of Outcomes

This Registry uses the term "birth defects" for outcomes sometimes referred to as “congenital anomalies.” For purposes of analysis, pregnancy outcomes will be dichotomized according to the presence or absence of birth defects. The latter group will be further categorized as: 1) Live births, 2) spontaneous abortions (i.e., pregnancy losses), and 3) induced abortions. This Registry has adopted a definition of a child with a birth defect as any live or stillborn neonate with a structural or chromosomal abnormality diagnosed before 6 years of age. The Registry will employ a conservative approach of including all defects, including minor ones, as congenital abnormalities. Therefore, conditions not appearing in the Centers for Disease Control and Prevention (CDC) Inclusion List may be classified as congenital abnormalities. All defects will be included in the “congenital abnormalities” category, regardless of whether or not the neonate is delivered alive, including structural defects in neonates delivered prior to 20 weeks of gestation or weighing less than 500 grams. However, CDC guidelines

disqualify as defects those findings that are present in infants delivered at less than 36 weeks of gestation and are attributable to prematurity itself, such as a patent ductus arteriosus or inguinal hernias. Infants with infectious conditions (e.g., neonatal sepsis) or biochemical abnormalities (e.g., hyperbilirubinemia) will be classified as being without congenital abnormalities unless there is a possibility that the condition reflects an unrecognized birth defect.

3.4. Exclusions

For this Registry, emphasis is placed on prospective registration of pregnancies. Although the Registry will encourage reporting of all known prenatal exposures to Twinrix, not all reports are appropriate for inclusion in the analysis of data.

Retrospective reports from patients and health care providers will also be received in the Registry. These outcomes will be reviewed and are helpful for detecting a possible pattern of defects. However, because there is no denominator from which risk can be calculated, these reports will be excluded from the analysis, although they will be summarized in the registry reports.

3.5. Analysis

Pregnancy outcomes will be stratified by the trimester of exposure, with an additional stratum for preconception exposure with no subsequent administration during pregnancy. Reports of multiple exposures (i.e., multiple administrations of Twinrix) during a pregnancy will be classified by the earliest trimester of exposure. When exposure occurs before and after conception, the exposure will be classified by the dose administered after conception. Gestational weeks will be counted from the date of the last menstrual period. The second trimester will be considered to begin at week 14, and the third trimester beginning at week 28.

The calculations of risk for birth defects will be made by dividing the number of infants with birth defects by the total number of infants with and without birth defects. Spontaneous abortions and induced abortions not including birth defects will be excluded from this calculation. An exact 95% confidence interval (CI) will be calculated using the software application Stata, version 8.2 (Stata Corporation, College Park, TX).

The risk in the general population of all birth defects meeting CDC criteria is approximately 3% (range 2%-5%) of live births [Centers for Disease Control]. The estimated risk cited in medical literature varies because of differences in case definitions, populations sampled, and ascertainment methods. The Collaborative Prenatal Project, using a broader case definition and prospective ascertainment, reported a frequency of 5-7% [Chung, 1975]. Most major structural defects originate during the first trimester of pregnancy, which is the critical time for organogenesis. For such defects, exposures occurring in the second or third trimester are not likely to be causally associated. However, for the sake of completeness, and to enable the

CONFIDENTIAL

assessment of possible increases in the frequency of birth defects, all defects will be included in the reports for this Registry.

Criteria for review of a specific individual report include: 1) was the timing of the exposure to Twinrix commensurate with the ontogenetic development of the organ(s) affected by the abnormalities; 2) was there another known or likely cause (e.g., preexisting genetic or chromosomal defect or exposure to a known teratogen); 3) was the congenital abnormality not previously described (i.e., was it new to medical science); 4) was there a unique constellation of defects (i.e., was there a new syndrome)? Criteria for review of aggregate data include: 1) was there a deviation from the expected frequency of all defects indicating an increase in the overall risk of defects; 2) was there a deviation from the expected frequencies of individual defects; 3) was there uniqueness (e.g., a pattern) of the abnormalities that is suggestive of a common etiology? Studies have shown the risk of spontaneous abortion is high early in pregnancy and decreases substantially from week 8 to week 28, yielding a cumulative estimated risk of 10-22% [Anderson, 2000, Fenster, 1997, Khattak, 1999, Osborn, 2000, Ventura, 2000, Wilcox, 1981, Wilcox, 1983, Wilcox, 1988, and Windham, 1997]. Calculation of risk of spontaneous pregnancy losses overall should not be attempted and cannot be compared to the incidence in the general population because pregnancies in this Registry are reported at variable and, occasionally, imprecise times. Also, pregnancy losses occurring early in gestation may not be recognized and/or reported.

While the Registry is limited to prospective reports, some pregnancy exposures are reported only following pregnancy outcome (retrospective reports). The Registry will also review each retrospective report involving a birth defect. In general, retrospective notification of outcomes following exposures to drugs or vaccines is biased toward reporting the severe and unusual cases, and is not reflective of the general experience with the drug. Moreover, information about the total number of exposed persons is unknown. Therefore, incidences of outcomes cannot be calculated from these data. However, a series of reported birth defects can be analyzed to detect patterns of specific congenital abnormalities and can identify early signals of new vaccine-associated risks. A separate section of each registry report will describe all abnormal outcomes of retrospectively reported cases.

3.6. Timing of Reviews

The initial two analyses of Registry data are planned to be performed when six and twelve months, respectively, of postmarketing data from the United States are available. Subsequent analyses will be annual.

3.7. Potential Biases

As reporting of pregnancies is voluntary, it is possible that even among prospectively-reported pregnancies there could be bias in type of pregnancies which are reported. For example, high-risk pregnancies may be more likely to be reported.

CONFIDENTIAL

The calculation of risk, which does not include spontaneous abortions or voluntary terminations for which no defects have been reported, may introduce bias. It is unknown what proportions of these pregnancies consist of potentially normal outcomes versus congenital abnormalities. GSK will attempt to obtain information on anomalies detected at the time of the outcome, but this may not be known to the reporting physician.

Those pregnancies that have reached estimated dates of delivery but for which outcome information was unobtainable will be considered lost to follow-up. It is possible that outcomes among pregnancies lost to follow-up could differ from those with documented outcomes. All attempts will be made to minimize this potential source of bias.

4. REFERENCES

1. Anderson AN, Wohlfahrt J, Christens P, Olsen J, Melbye M. Maternal age and fetal loss: population based register linkage study. *British Medical Journal* 2000; 320:1708-1712.
2. Centers for Disease Control and Prevention (CDC). Update on Overall Prevalence of Major Birth Defects.
3. Chung CS, Myrionthopoulos NC. Factors affecting risks of congenital malformations: Reports from the Collaborative Perinatal Project. Birth Defects Original Article Series 1975; Vol. 11, No. 10.
4. Fenster L, Hubbard AE, Windham GC, Waller KO, Swan SH. A prospective study of work-related physical exertion and abortion. *Epidemiology* 1997; 8:66-74.
5. Khattak S, K-Moghtader G, McMartin K, Barrera M, Kennedy D, Koren G. Pregnancy outcome following gestational exposure to organic solvents. *Journal of the American Medical Association* 1999; 281:1106-1109.
6. Mitchell AA, Cottler LB, Shapiro S. Effect of questionnaire design on recall of drug exposure in pregnancy. *American Journal of Epidemiology* 1988; 123:670-676.
7. Osborn JF, Cattaruzza MS, Spinelli A. Risk of spontaneous abortion in Italy, 1978-1995, and the effect of maternal age, gravity, marital status, and education. *American Journal of Epidemiology* 2000; 151:98-105.
8. Ventura SJ, Mosher WD, Curtin SC, Abma, JC, Henshaw S. Trends in pregnancies and pregnancy rates, United States, 1976-96, National Center for Health Statistics. Vital Health Stat 21, 2000.
9. Wilcox AJ, Treloar AE, Sandler DP. Spontaneous abortion over time: comparing occurrence in two cohorts of women a generation apart. *American Journal of Epidemiology* 1981; 114:548-553.
10. Wilcox AJ. Surveillance of pregnancy loss in human populations. *American Journal of Industrial Medicine* 1983; 4:285-291.
11. Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD, Scletterer JP, Canfield RE, Armstrong EG, Nisula BC. Incidence of early loss of pregnancy. *New England Journal of Medicine* 1988; 319:189-194.
12. Wilcox AJ, Horney LF. Accuracy of spontaneous abortion recall. *American Journal of Epidemiology* 1984; 120:727-733.
13. Windham GC, Von Behren J, Fenster L, Schaefer C, Swan SH. Moderate maternal alcohol consumption and risk of spontaneous abortion. *Epidemiology* 1997;8:509-51

CONFIDENTIAL

BIOLOGICAL CLINICAL SAFETY AND PHARMACOVIGILANCE

***TWINRIX*[™] PREGNANCY REGISTRY PROTOCOL**

ADDENDUM

16 January 2013

METHODS

Registration

When the pregnancy registry was started enrolment of subjects occurred by the Health care providers calling the telephone number PPD . To increase the rate of pregnancy registration, a web page (<http://pregnancyregistry.gsk.com/twinrix.html>) was created in 2004 with instructions for enrolling patients in the Registry. In addition, at the request of GSK, FDA posted a link to this web page on their Pregnancy Registry Website in 2005. In response to a 2008 request from FDA to facilitate enrolment, GSK initiated a dedicated toll-free number (PPD), where callers can receive assistance in the registration of pregnancies. Notice of this new toll-free number was posted on the GSK web page in January 2009; the new toll-free number was added to the United States Prescribing Information in early 2009.