Food and Drug Administration (FDA)

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Addressing Inadequate Information on Important Health Factors in Pharmacoepidemiology Studies Relying on Healthcare Databases; Public Workshop

Food and Drug Administration (FDA), in collaboration with the University of Maryland Center for Excellence in Regulatory Science and Innovation (CERSI)

May 04, 2015, 8:00am – 5:00pm

FDA Campus at 10903 New Hampshire Avenue

Building 31, Great Room A

Silver Spring MD

Background Summary

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I. Introduction

The safety profile of a new drug product at approval is largely determined from evidence drawn from pre-approval non-clinical and clinical trial data. After marketing approval, new safety signals emerge as the drug product become increasingly utilized in clinical practice by a broader and more diverse patient population who may differ in important ways from the patients who were studied prior to approval. Regulatory actions to update labeling, promote safe use and/or mitigate risks of drug products may be based on numerous sources, including drug utilization trends, spontaneous case reports, case series and post-approval clinical trials and observational studies. The US Food and Drug Administration (FDA) can require drug sponsors to perform additional safety studies or clinical trials when FDA becomes aware new safety information about a serious safety risk. Post-approval safety studies, which are generally observational, may reflect drug use patterns in the general population and have the ability to capture the clinical experience in a larger and more diverse population.

Observational post-approval studies may be conducted prospectively by recruiting and following patients for the outcome of interest, or retrospectively by analyzing large existing electronic healthcare databases. One major advantage of conducting observational studies retrospectively is the timely evaluation of safety signals to inform regulatory decisions. Other advantages include the availability of a large number of persons followed over time, the ability to include a broader and more representative population, and the absence of invasive recruitment and follow-up procedures associated with studies utilizing prospectively collected data. Drawbacks of studies conducted in existing electronic healthcare data sources include the absence of important covariates or health factors necessary to adequately evaluate the drug-outcome relationship. Regardless of which observational study is initiated, the ability to establish a causal association between exposure and outcome in an observational study is challenged by lack of randomization. In the absence of randomization, investigators often rely on design or analytical techniques such as matching, multivariate regression models, propensity and disease risk scores to account for factors that may confound the association between exposure and outcome. The performance

of these techniques is dependent on the availability of information on the potential confounding factors in the analytical data source. Despite the use of design and analytical tools to control for confounding, it is often not possible to rule out the influence of confounding by unmeasured or inadequately measured factors, particularly in light of often modest drug-associated increases in risk. Because observational studies are increasingly utilized as evidentiary sources for regulatory decisions, FDA is interested in ensuring that findings from observational research are minimally influenced by confounding factors.

The goal of this public meeting is to initiate discussions on creative strategies to improve the capture of potential confounders in studies relying on electronic healthcare databases including administrative (claims) and electronic medical record databases. The objective of this workshop is to engage in constructive dialogue among regulators, academicians, researchers, regulated industry and other stakeholders on creative strategies to improve the capture and availability of information on important unmeasured or poorly measured confounders as well as how to make inference of information from other sources on important covariates poorly captured or typically unavailable and discuss methodological considerations to minimize the influence of residual or unmeasured confounding in post-approval pharmacoepidemiology studies conducted in electronic healthcare databases.

II. Confounding in Observational Research, Brief Overview of Relevant Concepts [1]

For a causal relationship to be established between drug exposure (treatment) and the adverse event or outcome of interest, three pieces of information are necessary: the **outcome of interest** (the observed outcome status based on the individual's exposure status), the **drug exposure status** (exposed and unexposed) and each individual's **"counterfactual outcome"** for the population under study (the unobserved outcome status based on the individual's unobserved exposure status). While the outcome and exposure are observed in any experiment or study, the counterfactual outcomes are unobservable and are considered missing data. Because randomization assigns treatment status by chance, it ensures that the

missing counterfactual outcomes occurred by chance, given that the observed outcome is due to random treatment assignment. In ideal randomized studies, randomization allows for exchangeability across comparison groups, meaning that the counterfactual outcome and the exposure status are independent; therefore the counterfactual risk in both the exposed and unexposed groups is equivalent.

In pharmacoepidemiology studies, treatment assignment is not randomized and may be determined by many factors. If any of these factors also affects the risk of developing the adverse event of interest, then the effect of the factor on the adverse event and the effect of the exposure on the adverse event become mixed or, in other words, the factor confounds the association between treatment and adverse event. Confounding arises when the treatment and adverse event share a cause, resulting in a violation of exchangeability across comparison groups. In graph theory, the path that links the treatment and the outcome via the common cause is referred to as the backdoor path. The backdoor path can be blocked by conditioning on all measured covariates that are non-descendants of the treatment i.e. covariates that are not affected by the treatment (*referred to as the back-door criterion)*. In theory, the backdoor criterion represents a universe of several back-door paths; some of which are measurable in the analytical database of interest and others which are unmeasurable or completely unknown. While the unknown back-door paths remain a major limitation of all observational studies, the strength of evidence from pharmacoepidemiology studies is directly related to the ability to eliminate the known, measurable backdoor paths. It has been suggested that some (known and unknown) back-door paths are weak and thus exert a minimal impact on the biased estimates or that several (known and unknown) strong backdoor paths eliminate each other (by acting in opposite directions) hence resulting in an overall weak net bias. Therefore, the primary focus of this workshop will be to initiate discussions on strengthening the information of the known backdoor paths to improve the strength of evidence for causality derived from pharmacoepidemiology studies.

III. Select Examples

In this section, selected examples are provided to illustrate the challenges in using administrative databases to conduct studies to evaluate the association between a drug exposure and an adverse event when data on specific health factors are not captured adequately. The purpose of including these examples is not to provide a discussion regarding the evidence, or lack thereof, for potential safety signals associated with specific treatments and their regulatory implications. Instead, these examples are simply meant to provide a framework for methodological discussions involving challenges associated with the use of healthcare databases to evaluate the safety of regulated products.

III.1. Medications during pregnancy and neural tube defects in the offspring

Neural tube defects (NTDs) refer to a group of congenital anomalies of the central nervous system that result from failure of the neural tube – the precursor of the central nervous system - to close during embryonic development. The most severe NTDs are anencephaly and spina bifida myelomeningocele, with prevalence estimates varying by calendar time and geography, ranging between 4 to 6 cases per 10,000 live births in the United States[2]. Pregnancies with an affected fetus may result in spontaneous or elective pregnancy termination, thus estimates based on live births are likely to under-represent the true prevalence of NTDs.

Genetic and environmental risk factors of NTDs have been identified in the literature[3 4]. Among environmental risk factors, maternal folate deficiency is the most notable risk factor influencing risk of NTDs[5], which has led to public health measures of mandatory fortification of certain foods with folic acid in 1998[6] and prenatal folate supplementation programs to reduce risk of NTDs. Other established environmental risk factors include maternal history of pre-gestational diabetes, pre-gestational obesity, and intake of certain medications during pregnancy, including the anticonvulsant valproate[4]. The most relevant risk period of exposure is during neurulation, the embryonic process that leads to the development of the neural tube estimated to occur between 18 days and 4 weeks after conception.

It has been hypothesized that certain medications that affect availability of folic acid may increase risk of NTDs[7 8]. Examples include products containing trimethoprim-sulfamethoxazole, which exert their antibacterial effects by interfering with the biosynthesis of nucleic acids and proteins essential to many bacteria. Specifically, trimethoprim blocks the production of tetrahydrofolic acid from dihydrofolic acid; sulfamethoxazole inhibits bacterial synthesis of dihydrofolic acid[9], suggesting a potential pathway for the role of these anti-infectives in the risk of NTDs.

Several studies in the published literature have evaluated the association between use of trimethoprim-sulfamethoxazole/sulfanamide during pregnancy and risk of NTD in the offspring, with conflicting results (examples of studies suggesting an increased risk include references [7 8 10 11]; examples of studies suggesting no association include [12 13 14]). Almost all of these studies obtained information on exposures during pregnancy and some potential confounders through maternal interviews. In most cases, information on exposure status was obtained retrospectively and bias due to differential recall of exposure between mothers with and without infants with congenital deformities cannot be ruled out, although at least one study included malformed controls in attempt to address this issue[7]. Small sample size and selection bias due to differential participation rates or differential criteria employed between cases and controls are additional potential limitations in several studies.

Studies conducted in large, existing electronic healthcare databases that are able to link data between mothers and offspring are, at least in theory, promising as these may circumvent important potential limitations of previous studies. Relying on medical or pharmacy records to obtain information on medication exposure during pregnancy avoids bias due to differential exposure recall between comparison groups. Additionally, these studies do not rely on enrollment of patients and are instead able to include all eligible patients thereby minimizing potential for selection bias. However, a crucial limitation of electronic healthcare databases is the absence of important covariates, such as maternal folic acid intake during pregnancy (e.g., over-the-counter supplementation and folic acid from food sources) and under-ascertainment of information on folate deficiency. Other important covariates include alcohol use during

pregnancy, smoking during pregnancy, family history of congenital anomalies, none of which are adequately captured in most existing claims databases. Lack of adequate data on certain health factors, including folic acid intake or folate deficiency during pregnancy, among others, may result in biased or uncertain estimates of the effect of medication exposure during pregnancy on risk of NTD in the offspring.

III.2. Drospirenone-containing contraceptives and venous thromboembolism

Drospirenone (DRSP)-containing oral contraceptives (OCs) are derivatives of female endogenous hormones (estrogen and/or progestin) acting primarily as extensions of the numerous physiological processes associated with these hormones. DRSP 3mg/Ethinyl Estrogen (EE) 20 mcg was approved for the prevention of pregnancy in March 2006. Shortly afterwards in October 2006, it was approved for the treatment of symptoms associated with PMDD in women who choose to use an OC for contraception. In January 2007, it was approved for the treatment of moderate acne for women who were at least 14 years of age, only if the patient desired an OC for birth control.

Thromboembolic events including venous and arterial thromboembolism, although rare, have been observed more frequently in combined oral contraceptive (COC) users compared to non-users. The venous thromboembolic event (VTE) endpoint includes two major diagnoses among others: deep vein thrombosis (DVTs), referring to clots associated with the lower extremities, and pulmonary embolism (PE) in cases where the clot moves and resides in the lungs. The arterial thromboembolism (ATE) endpoint refers to thromboembolism in large arteries presenting most frequently as acute myocardial infarction (AMI) or as stroke. Evidence suggests that the estrogen-component of the COCs is associated with the increased risk of VTEs or ATEs observed. The first COCs contained high levels of estrogen, more than 50 mcg estrogen derivative, frequently ethinyl estradiol (EE), and were combined usually with a norethindrone progestin, the first generation. COCs containing high EE levels are no longer being manufactured. Newer generation COCs typically contain between 20 and 35 mcg EE. Progestins, a

hormone important in maintaining the menstrual cycle, are presumed to counteract the cardiovascular risk to different degrees depending on the type of progestin. To improve the overall cardiovascular risk profile for COCs, newer progestin molecules were developed concurrently with the estrogen dose reduction. These include the second generation products levonorgestrel and norgestimate and the third generation product desogestrel. Newer progestins are arbitrarily referred to as fourth generation and include drospirenone and norelgestromin. While DRSP's association with lack of weight gain and antimineralocorticoid activity may have been perceived as a benefit in terms of cardiovascular risk, the potential increased risk of arrhythmia from hyperkalemia was a major concern at the time of approval. As with all OCs, concerns about the possible increased risk of VTE and ATE prompted the labeling of DRSP consistent with other COCs. With increasing post-market use, several studies evaluating the association between DRSP OCs and VTE emerged with conflicting findings. Studies [15] [16]based on personal interviews; *i.e.* prospectively conducted studies, showed no increased risk of VTE when compared to other frequently prescribed combined oral contraceptives (COCs) or when compared to levonorgestrel containing OCs only. On the other hand, all studies [17] [18] [19] [20] [21] [22] [23]that used electronic healthcare or claims-based records, with the exception of the one study (the Ingenix study) that used propensity score matching, reported an increased relative VTE risk (≥ 1.5) irrespective of validated outcomes. Because administrative or electronic data sources capture all use and lack adequate information on important confounders such as family history, body mass index: (BMI), lifetime use of hormonal contraceptives and smoking, it remains unknown whether the observed increased risk is primarily due to inadequate adjustment of these confounders or other population characteristics that cannot be measured in electronic healthcare databases.

IV. Workshop Objectives

With the objective of engaging the scientific community in discussions regarding how to improve information on health factors in studies conducted in electronic healthcare databases, the Food and Drug

Administration (FDA), in collaboration with the University of Maryland Center for Excellence in Regulatory Science and Innovation (CERSI), is organizing a workshop entitled "Addressing Inadequate Information on Important Health Factors in Pharmacoepidemiology Studies Relying on Healthcare Databases; a Public Workshop." The purpose of the public workshop is to initiate a constructive dialogue among regulators, academicians, researchers, regulated industry and other stakeholders including the general public on potential strategies to improve information on important health factors in pharmacoepidemiology studies conducted in existing electronic healthcare databases to evaluate the safety of pharmaceutical products in the post-approval setting. This workshop will consist of a series of presentations describing selected work related to innovative strategies to improve information on important health factors that are unavailable (unmeasured) or inadequately captured in electronic healthcare databases with ample time for discussion among panel members and the public. The workshop agenda and topics for panel discussions are found in the sessions below.

V. Workshop Agenda

This workshop is scheduled to take place, May 04 of 2015 from 08:00 to 17:00. The agenda is detailed below.

[8:00] Registration

[8:30] Welcome remarks, Introduction of panel members

[9:00] Session 1: Introduction

Presentation*:* Background and objectives (E. Eworuke, S. Pinheiro, FDA)

Presentation : Overview of confounding (F. Shaya, UMD)

[9:45] Clarifying questions

[10:00] Morning Break

[10:15] Session 2: Creative Methods to improve confounding information

Theme 1: Supplementing data with surveys and linkages

Presentation: Use of external information to evaluate comparability of cohorts (Kaiser database, CMS beneficiary surveys), (D. Graham, FDA)

Presentation: Data linkages to obtain information on driving conditions in a study evaluating exposure to ADHD medications and motor-vehicle accidents (A. Winterstein, U of Florida)

Presentation: Use of surrogate measures: striking a balance between information added and introduction of measurement error. This presentation discusses linking aggregate data on confounders from external sources to existing cohorts extending the concept of administrative databases. (J. Major, FDA)

Presentation: Working in settings of limited resources: 2-phase design to improve efficiency of sampling. (S. Dublin, GHRI)

Presentation: Looking ahead, using mobile devices to enhance information on EHR (W. Riley, NIH)

[11:30] Clarifying questions

[12:00] Lunch break

[13:00-14:00] Panel Discussions

[14:00] Session 2, continuation

Theme 2: Making greater use of the data at hand

Presentation: Text mining strategies using the VA system (F. Cunningham, VA)

Presentation: The role of study design to reduce the potential for confounding (T. Sturmer, UNC)

Presentation: Implications of and solutions for covariate measurement error and differential covariate measurement across treatment groups (E. Stuart, J Hopkins)

Presentation: Improving the reliability, transparency, and reproducibility of database research without transmitting patient-level databases (S. Schneeweiss, HMS)

[15:00] clarifying questions

[15:15] Afternoon break

[15:30-14:45] Session 3, Panel Discussions

[16:45] Wrap-up and summary of discussions (FDA and UMD)

[17:00] Meeting adjourns

VI. Topics for Panel Discussions

1. Consider the example discussed earlier on drospirenone-containing contraceptives and VTE. What strategies (discussed or not discussed during this workshop) appear most promising to improve information on covariates that are not completely or reliably captured in healthcare databases, including body mass index, smoking, family history? We encourage you to think creatively.

2. Consider the example briefly discussed regarding medication during pregnancy and neural tube defects. What strategies (discussed or not discussed in this workshop) appear most promising to improve information on variables not available in healthcare databases such as folic acid (supplementation beyond prescription; e.g. over the counter, dietary intake, levels)? We encourage you to think creatively.

3. Are there additional methodologies beyond what was discussed (e.g. data linkages, leveraging study designs, considering the effects of misclassified variables) that can help minimize the influence of residual and unmeasured confounding?

4. How can we move in the direction of improving information on important confounding factors (those that are incompletely captured and those that are not available) in pharmacoepidemiology studies?

5. How can we minimize bias introduced by confounding vs. biases potentially introduced by strategies employed to improve confounding (e.g. analyses conducted in patients who have data on confounders)

6. Given the modest nature of most RRs in pharmacoepidemiology studies, how/when can we feel confident that the results are not meaningfully influenced by residual or unmeasured confounding?

VII. References

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