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April 18, 2011

Dockets Management Branch (HFA-305)
Food and Drug Administration
5600 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2011-D-0057: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the "Draft Guidance for Industry and FDA Staff on Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets". BIO supports the Agency's efforts to fully utilize new electronic health care data sources for post-approval pharmacoepidemiologic studies. These new data resources offer great promise to revolutionize the practice of pharmacovigilance with more timely and cost-effective methods for conducting post-market studies, but great care must be taken to minimize the potential for confounding and bias. We hope the Draft Guidance will provide additional transparency in scientific exchange between FDA in Sponsors when initiating appropriate pharmacoepidemiological studies in a regulatory context. With this goal in mind, we request clarification of several aspects of the Draft Guidance, particularly around the process for submitting and reviewing study protocols.

BIO represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

BIO commends FDA for developing this comprehensive document to identify pharmacoepidemiologic safety study best practices, consistent with the PDUFA IV commitment. BIO also thanks the Agency for reviewing our previous comments on this topic.[1] The scope of this Guidance is well-circumscribed and the scientific recommendations are consistent with best expected practices and state of the art in the field. The purpose, as explicitly stated in the introduction (lines 20-23 and 33), is to ultimately optimize FDA's review of protocols and final reports that are submitted to the Agency for this type of study. FDA has wisely narrowed the focus of this Guidance to apply specifically to the use of electronic healthcare information, which differentiates it from already well-established but more general best practice guidance in the field (FDA 2005 guidance, International Society of Pharmcoepidemiology (ISPE) guidelines and STROBE (STrengthening the Reporting of OBservational studies in Epidemiology)).

From this perspective, there are several recommendations that BIO member companies can provide on the Guidance structure and content that are based on our experience with the process of designing and implementing pharmacoepidemiologic studies that have been reviewed by the Agency in the past. There are also several statements that are found to warrant additions or further clarifications, which are mentioned in this response.

GENERAL COMMENTS:

I. The Role of Pharmacoepidemiological Studies in Determining Causality, Association, and Magnitude of Effect

The emphasis throughout the document should be that the goal of these studies is to identify potential causal associations of drugs and estimate their magnitude. Therefore, when reporting any finding the extent to which it can be interpreted as a causal effect should be discussed. The document should also more clearly distinguish between causal effects and associations. For example, in database studies the validation of drug exposure is limited, and hence, attributing outcomes to drug exposure based on an association between prescription claims and medical claims can be misleading. Additional research efforts in this area are needed. In the Introduction of the Draft Guidance, we suggest a change from "to assess the risk attributed to a drug exposure" to "to assess the risk associated with a drug exposure" (line 25).

In addition, the document seems to circumvent the possibility of using these types of studies to provide evidence of a lack of an association between the drug and the event (which may have been seen spuriously during clinical trials). We request that the Agency reconsider this position.

[1] BIO Comments, "Developing Guidance on Conducting Scientifically Sound Pharmacoepidemiologic Safety Studies Using Large Electronic Health Care Data Sets", June 6, 2008, http://www.bio.org/reg/20080606.pdf

II. Process and Timing for Protocol Review

To promote transparency in the conduct of pharmacoepidemiology safety studies, the Guidance states that "FDA encourages industry to inform FDA of all pharmacoepidemiologic safety studies; to submit plans and protocols for such studies before study initiation; and to submit comprehensive final reports with detailed methods and results to FDA in a timely manner." (lines 43-45) While the Draft Guidance is clear on the expectations regarding the submission of protocols and observational safety studies, there is no information on the process by which FDA will review and comment on these study protocols. What are the specific timelines and expectations regarding feedback and approval? Who will provide feedback on the methodologic approaches of the study and how will discrepancies and disagreements be resolved?

Based on BIO member experience, FDA has reviewed final draft protocols and provided helpful feedback that requires incorporation into the final study protocol. However, the Draft Guidance appears to only refer to submission of final study protocols. Review of a final study protocol and provision of extensive regulatory feedback at the time of study implementation would be quite disruptive. BIO would support regulatory review at the final draft protocol stage to facilitate timely FDA review, with final protocol submission to the Agency upon its completion or at a mutually agreed upon time. If this 2-stage review is in actuality a general FDA practice, then it should be explicitly stated in the Guidance.

A clear, consistent process for protocol submission and review will minimize the potential for this process to significantly prolong the timeframe needed to complete studies and analyses, thereby delaying the availability of results that may affect future regulatory and development activities.

III. Communication with the Sponsor in Advance of an FDA-Initiated Study

In the spirit of transparency and scientific dialogue to advance the body of evidence around a particular product's benefit/risk profile, we also request that FDA communicate with the Sponsor when developing the Agency's own protocol for a pharmacoepidemiological study using large healthcare data sets in a regulatory context. We note that FDA has access to a number of large healthcare data sets, such as Medicare claims data or electronic health records databases that are occasionally used for independent FDA research on potential safety signals. Product Sponsors should have adequate insight into FDA's process and rationale for selecting a particular study protocol so that there is opportunity to discuss the most appropriate methodology to further evaluate signals of serious risk around a given product. BIO member company experience suggests that interactions between FDA and Sponsors will encourage a selection of a study methodology that will result in the most valuable and medically relevant information for patients, physicians, and regulators.

BIO suggests that the Guidance should discuss a standard process or timeline for this FDA-Sponsor interaction. BIO also would like to discuss with FDA a process for Sponsors to access the database utilized in FDA-initiated pharmacoepidemiological studies so that conclusions can be replicated and validated.

IV. Scope of Recommended Protocols Submissions to FDA

Additionally, we request that FDA clarify the scope of the type of studies requiring FDA review. It is not immediately obvious whether "…all pharmacoepidemiologic safety studies…" (line 43) includes non-regulatory requested (*internally initiated*) studies or studies requested by other regulatory agencies. We note that many of these Sponsor-initiated studies are hypothesis generating in nature and are not intended for regulatory purposes or to provide conclusive scientific evidence.

BIO recommends that the scope of the recommendations should cover studies that are elements of regulatory commitment to the FDA only. We request that FDA clarify that these statements pertain to those studies that are agreed upon as part of a postmarketing study requirement or commitment (PMR/PMC) with the FDA or as part of a risk management plan. We also suggest that the Guidance state that the scope of the recommendation for protocol submission do not extend to studies that are descriptive in nature, hypothesis generating, assess a safety issue outside of the scope of a PMR/PMC, or are conducted as part of a comparative effectiveness assessment.

We also recommend greater clarity in the Guidance around the difference between hypothesis-strengthening and hypothesis-testing studies and that additional examples be provided.

V. Non-Disclosure of Study Protocols

BIO also notes that the Draft Guidance is silent on whether the study protocols submitted to FDA will be held confidential or publically disclosed. Certain study protocols may include information that is proprietary or confidential in nature and premature disclosure could undermine the competitive standing of the Sponsor. Therefore, BIO encourages FDA to revise the Draft Guidance to state that study protocols will not be publically disclosed.

Consistent with the FDA Amendments Act of 2007 (FDAAA) and Congressional intent, manufacturers are already required to register and submit results information for "applicable clinical trials" to the ClinicalTrials.gov database. An applicable clinical trial is defined by FDAAA to include controlled, clinical investigations, other than Phase 1 investigations, of a drug or device subject to FDA regulation. Observational and exploratory studies are excluded from this requirement, a significant protection of confidential proprietary information. However, many Sponsors choose to register these studies on a voluntary basis when proprietary information is not involved.

VI. Submission of Preliminary Feasibility Analyses

In Section IIIC on Study Approach Considerations, FDA encourages investigators to briefly describe any alternative study approaches and databases they considered before arriving at the proposed approach and to clarify why those proposed alternatives were neither feasible nor optimal in the context of answering the specific study question (lines 223-226). However, we note that contracted vendors such as Contract Research

Organizations (CRO) or Academic Research Organizations (ARO) that are often responsible for the preparation of the study protocol may not have been involved in conducting the feasibility assessment. Many pharmacoepidemiology studies are outsourced by biotechnology and pharmaceutical companies, which involves relying on the selected CRO for the development of the study-specific protocol that is focused on the scientific question of interest (with scientific input and oversight from the company). The CROs independently implement the study and prepare final reporting of the results.

It is therefore of concern that this Guidance recommends inclusion of preliminary feasibility study details and rationale for decision making at the level of specific databases, methodology and approaches considered and ruled out for the study. In the situation of outsourced studies, as recommended, these details would have to become part of the study protocol.

We also suggest that these details may well be of a strategic and confidential nature, and at the point of final study protocol preparation are at best contextual and quite peripheral to the study. For example, a response from a CRO to a Sponsor's Request for Information (RFI), which is often proprietary information belonging to the CRO provided under a Confidentiality Agreement, is often an important consideration and the underpinning for that manufacturer's decision on vendors' databases, study design, analytic plan, etc. Including specific detail on all data, methods, and other essential features considered in a final study protocol, as well as the rationale for ruling them in or out for the study, poses concerns given the sensitive nature of this information.

We request that FDA specify whether this information may be included instead in a briefing document distinct from the protocol. Under this alternative proposal, Sponsors could segregate out FDA's recommendations in this regard from the narrow information specific to the study at issue, which is traditionally included in study protocols. The scope of considerations and rationale for decision making could be included in a briefing document accompanying a draft final protocol submitted for review and feedback by the Agency. The final protocol would then incorporate study-specific feedback and be submitted at completion to the Agency.

VII. The Importance of Conducting Preliminary Pilot Studies and Data Assessments

We ask FDA to consider a adding a separate category in Section V. Best Practices – Study Design to highlights the importance of conducting preliminary pilot studies and data assessments. These voluntary, Sponsor-initiated assessments can help Sponsors to better understand the study population(s) and sample size implications, evaluate the data source and its limitations, identify potential confounding factors in the study population, and define drug and outcome variables before finalizing the protocol.

VIII. Case Specifications and Outcome Validation:

Evaluation of index case code specifications and formal validation of outcomes are recommended, as is the incorporation of the information gleaned through these processes

into the study protocol and analysis plan; if necessary, the modifications would need to be submitted as a final protocol amendment (lines 734-736, 182-186). Encouragement for pilot studies to evaluate case specification ahead of the finalization of a study protocol so that findings can inform this specification might be a worthy recommendation that would help minimize the need for amendments, as would be early conduct of feasibility or preliminary studies (lines 229-230).

For outcome validation, a plan to analyze only those study outcomes that were medically validated and adjudicated poses no significant difficulties. However, we request that FDA consider clarifying whether ascertainment or validation of other important variables should also be conducted (*e.g.*, confounding variables). Consideration of other ways of using validated data or findings from sensitivity analyses, such as for context for the interpretation of findings, without requiring incorporation of the information into the analytic plan via protocol amendment, should also be provided.

BIO supports the validation of outcomes as a best practice, but we recognize that in some instances it may not be practical or feasible to validate certain outcomes. This should not always preclude the study from being conducted if the study can be informative despite this limitation. Indeed, the Draft Guidance also suggests that "For studies without outcome validation, the investigator should provide appropriate justification of the outcome definition used." (lines 728-730).

IX. Quality Assurance (QA) / Quality Control (QC)

This Draft Guidance provides a great deal of guidance on QA/QC procedures. However, data holders rarely disclose completeness of data capture particularly when data reporting is voluntary (*e.g.*, inpatient medical procedures). Therefore, the recommended QA/QC procedures are beyond data users' control. Since the Draft Guidance addresses best practices in using electronic health data sets, we recommend FDA consider generating a separate guidance for the best practices of generating electronic health data, and move the sections IV-E and VI-G to the separate guidance.

It is also not clear whether the FDA is referring to the use of simulated data to assess the analytical performance of the statistical methods used or simple replication of analysis using different methods. We request that the Agency provide more specific guidance on the types of sensitivity analyses considered to be essential.

X. Statistical Analysis

Section VI on "Best Practices – Analysis" states that "In the study protocol, investigators should include a prespecified analysis plan that addresses the specific study objectives. The plan should specify primary and any secondary analyses. If investigators plan to perform ***preliminary analyses***, they should prespecify the plan." (lines 792-794) Given the detail that can go into the analytic plan, we suggest that it be standard practice for there to be a stand-alone analytic plan separate from the protocol, with only the top-level analytic details going into the protocol. A similar process is utilized in the context of

drug development. Therefore, we suggest that the formal statistical analysis plan be separate from the protocol.

Additionally, we question if primary and secondary analyses have the same meaning in observational studies as they do in randomized controlled trials (*i.e.,* whether this distinction is meaningful in observational studies) We suggest that the concept of primary and secondary analyses be eliminated in the context of observational research guidelines.

XI. Standardized Processes for Contracting with Certified CRO/ARO

While outside of the scope of this particular Guidance, industry, FDA, and CROs should evaluate opportunities to standardize the process for initiating studies conducted by contracted venders to enhance efficiencies. For example, CROs/AROs and other relevant researchers could create a voluntary, consolidated repository of CRO/ARO capabilities that contain information such as expertise, credentials, experience with specific data sources, and experience for ensuring quality assurance and quality control measures.

Alternatively, rather than having to make specific requests from vendors for every study commissioned, perhaps vendors should develop recommendations that would expedite the process of protocol development and enhance compliance with the Guidance recommendations. For example, vendor protocol templates could have study team expertise and credentials (lines 246-254) or a section on the vendor's quality assurance and quality control processes that are requested (lines 412-429). Some of the requests regarding approval or denial of claims (lines 292-294) that reflect health plan-specific policies may also be made available by the vendors ahead of time.

CONCLUSION:

BIO appreciates this opportunity to comment on "Draft Guidance for Industry and FDA Staff on Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets". We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Andrew J. Emmett
Managing Director, Science and Regulatory Affairs
Biotechnology Industry Organization (BIO)

SPECIFIC COMMENTS

LINE	SECTION	PROPOSED CHANGE
I. INTRODUCTION		
Lines 20-25:	"The guidance includes recommendations for documenting the design, analysis, and results of pharmacoepidemiologic safety studies to optimize FDA's review of protocols and final reports that are submitted to the Agency for these types of studies."	By implication of this sentence, no post hoc evaluations are to be considered. We recommend that the Guidance clearly distinguish between (1) primary and secondary hypotheses identified in the protocol and (2) exploratory analyses (hypotheses) generated as a result of observations from the primary and secondary hypotheses.
Lines 43-45:	"FDA encourages industry to inform FDA of all pharmacoepidemiologic safety studies; to submit plans and protocols for such studies before study initiation; and to submit comprehensive final reports with detailed methods and results to FDA in a timely manner."	As discussed in the general comments, please clarify that these statements pertain to those studies that are agreed upon as part of a PMR/PMC or risk management plan only. Additionally, please confirm that these recommendations do not include studies that are descriptive in nature, hypothesis generating, assessing a safety issue outside of the scope of a postmarketing commitment, or are conducted as part of a comparative effectiveness assessment.
Line 48, footnote #4:	"More specifically, the use of electronic healthcare data sets for hypothesis-generation (signal detection) or hypothesis-strengthening (signal strengthening), which is an intermediate step between hypothesis-generation and hypothesis-testing, is beyond the scope of this guidance."	Pharmacoepidemiologic research may often be considered hypothesis-strengthening, rather than hypothesis-testing. We recommend greater clarity around the difference between hypothesis-strengthening and hypothesis-testing and request additional examples.
II. BACKGROUND		
Lines 67-69:	"This evidence mostly emerges from one or more of the following data streams: randomized controlled trials	We note that not all clinical trials are randomized and controlled. However, safety signals also can be detected

	(RCTs), spontaneous adverse event case reports, or pharmacoepidemiologic safety studies."	in nonrandomized and uncontrolled trials.
Line 75:	"…overall conclusion regarding the relationship of the risk of the drug and reassessment of benefit and risk."	The relationship mentioned is not defined for the drug relative to something else. Please provide a definition.
Lines 86-88:	"However, because drug-related adverse events have the potential to broadly affect the public health, there is often an urgency to take regulatory action to address drug safety issues based on the available evidence, even if the data are less than optimal."	Please consider providing examples of when "...data are less than optimal."
Lines 92-93:	"As described in this guidance, the best practices for the conduct and reporting of pharmacoepidemiologic safety studies using electronic healthcare data are intended to facilitate a more independent interpretation of findings from these studies."	It is not clear what FDA means by "a more independent interpretation of findings." The term "independent" implies a lack of conflict of interest, but there is little about this in the document. We are not sure how the Guidance enables independence in the interpretation of findings. BIO suggests replacing "independent" with "a scientifically valid interpretation…" "a scientifically valid interpretation of finding"
Lines 143-149:	"The Consolidated Standards of Reporting Trials (CONSORT) statement (Moher, et al.), created to improve clinical trials research reporting and subsequently supported by medical journals, serves as an example of how basic reporting standards can improve the quality of reports on *clinical* trials. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (von Elm, et al.) provides guidelines for reporting *observational* studies.7 STROBE was created to address the fact that there is often missing information in published observational epidemiologic studies (von Elm, et al. 344)."	There is no mention of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP®) guidance, Checklist of Methodological Standards for ENCePP Study Protocols that was released last year. (http://www.encepp.eu/standards_and_guidances/index.html). We recommend that this should be added, with the remit of such guidance documents to provide the latest available information to colleagues. Industry is now conducting multi-database studies globally – harmonization of guidance (International Society for

		Pharmaceutical Engineering /FDA/ENCePP) will help, starting with including latest guidance in each document. Please add detail on ENCePP
III. BEST PRACTICES—GENERAL CONSIDERATIONS		
Lines: 176-178:	"Investigators should submit protocols to FDA before study initiation and final reports upon completion for all pharmacoepidemiologic safety studies using electronic healthcare data."	As discussed in the general comments, please clarify that it is not the intent of this guideline to recommend that all observational safety study protocols be submitted to FDA before study initiation.
Lines 181-183:	This provision states that: "All those involved in developing the protocol and their roles should be specified. **All of the elements described within this guidance should be addressed in the protocol.** Any changes to the initial protocol after initial collection of data should be justified and documented."	Regarding the statement, "All of the elements described within this guidance should be addressed in the protocol", some of the elements relate to interpretation of findings that are not typically part of a protocol. While "Study Approach Considerations" and "Study Team Expertise and Credentials" are important, they do not belong in the protocol. These elements are not included in protocols for randomized controlled trials. We request that FDA clarify which elements should be addressed in the protocol. Additionally, it is unclear where "any changes to the initial protocol after initial collection of data should be justified and documented." We recommend inserting the statement "in an amended protocol" and a "final report". In an amended protocol and a final report, any changes to the initial protocol after initial collection of data should be justified and documented. Finally, we also suggest the inclusion of wording highlighting that because of the nature of observational research, multiple protocol amendments are more likely to occur than with clinical trials.

Line 188:	**"A. Title and Detailed Study Summary"**	We suggest the term "Structured Study Summary" instead of Detailed Study Summary.
Lines 197-206:	This section discusses several bulleted elements useful to summarize the key points of these types of studies.	Please specify which key points are relevant to study protocol and which are relevant to report.
Lines 203:	"Methods to control for sources of bias."	We suggest that confounding factors should also be controlled.
Lines 215; 260-262:	"Based on this background and the identified gaps in evidence, investigators should establish concise study objectives and specific, feasible hypotheses." "In particular, findings of no association between the drug and safety outcome of interest should be presented in the context of the initial statistical power calculations; investigators should attempt to determine the level of risk that can be ruled out, given the study findings."	Often for an observational safety study, one would like to be able to rule out an association between a drug exposure and outcome, which is much harder to evaluate than a hypothesis that there is an increased risk associated with drug exposure. The concept or meaning of study power to exclude risks greater than a prespecified value, particularly in a setting where there may be unmeasured confounding, is challenging. Observing an association within a pre-specified range of the null does not necessarily constitute proof of no harm (just that the true effect may be small).
Line 259:	"When interpreting findings, investigators should summarize the key results of the study, including the main measures of effect (including the absolute risk estimate if possible)."	The statement "including the absolute risk estimate if possible" implies that both relative risk and absolute risk should be included as the main measures of effect. This should be more explicitly stated. We suggest revising to: "including ~~both~~ the relative risk estimate and the absolute risk estimates if possible".
Lines 259-261:	"In particular, findings of no association between the drug and safety outcome of interest should be presented in the context of the initial statistical power calculations…"	Similar to the comment above, identification of statistically significant positive associations should be interpreted in the context of the power of large database studies, especially for the assessment of relatively common outcomes. We suggest including a statement that small differences, while statistically significant because of large sample sizes may not be clinically

		relevant or causal in nature**.** Please consider revising to: "findings of no ~~association between the drug and safety outcome~~ statistically significant association
Line 264:	"Because statistical significance can be easy to achieve in large electronic data sets and, alone, does not exclusively determine the importance of the findings, it is critical for clinical significance to be considered when interpreting findings."	We suggest adding a sentence from 2008 Good Pharmacoepidemiology Practices Guidelines stating that "effect measures should not be described as significant or not significant". Then continue the sentence with the focus on clinical relevance. Please consider revising to: "Because statistical significance can be easy to achieve in large electronic data sets and, alone, does not exclusively determine the importance of the findings, effect measures should not be described as significant or not significant".
Lines 270-271:	"Investigators should also discuss the limitations of the database and design and their impact on generalizability."	As part of the discussion of the limitations of the database, it should be noted that percentages of missing data, as well as the percentage of data requiring the use of special conventions, should be provided by the Sponsor.
Lines 271:	"Investigators should discuss key biases…."	Please consider revising to: "Investigators should discuss key biases and confounding factors"
Lines 292-298:	"…it is important to understand this limitation to use the data systems appropriately for investigations of a drug's safety. For example: • Administrative claims data are generated to support payment for care; policies governing the approval and denial of such payments should be considered before using these data for investigations. • EMR data are generated in the process of	We request that FDA provide more comprehensive considerations on the criteria to be used for assessing "appropriateness" of data sources. The current Draft Guidance provides two examples that appear to be fragmented.

	providing routine clinical care; therefore, it is important to consider guidelines for patient care and common clinical practices within that healthcare system that will influence the collection of data and any investigation based on the data."	
IV. BEST PRACTICES—DATA SOURCES		
Lines 327-363:	**"B. Enrollment and Comprehensive Capture of Care"**	Section B is very important as it stresses the need for a form of patient / subject accountability. The need to "trace" subjects through the times that they are in, out, and maybe back in again is very important and needs to be stressed.
Line 345:	"In addition, patients in the United States do not typically "enroll" in physician practices, but rather see physicians as needed or as their insurance coverage allows."	We suggest rephrasing "as their insurance coverage allows" to: "as channeled by their insurance coverage ~~allows~~."
Line 347:	"Therefore, when using an EMR data source, it is crucial to employ and describe methods to ensure complete observation and capture of patient care over time to facilitate the likelihood that all exposures and safety outcomes of interest will be captured."	In particular, it should be made clear by the Sponsor when the absence of information regarding certain outcomes is treated as the absence of the outcome, in the analysis. (This is covered in lines 850-852 but might be good to include here also.)
Lines 349-350:	"In the United States, primary care-based EMR networks may not capture hospitalizations or visits to specialists. If these are events of interest, investigators should specify how these events will be captured."	We welcome additional guidance on how a Sponsor would go about capturing these events of interest.
Line 369:	"In situations where use of a data source from a country other than the United States is proposed, it is important to provide: • A discussion regarding why the data are most appropriate to address the specific hypotheses;"	We suggest deleting the word "most" in the statement "A discussion regarding why the data are most appropriate to address the specific hypothesis." as one could never prove that the data are most appropriate. We believe it is adequate to discuss why the data are appropriate. We

		suggest the sentence read: "A discussion regarding why the data are ~~most~~ appropriate to address the specific hypothesis."
V. BEST PRACTICES—STUDY DESIGN		
Line 412:	"**E. Quality Assurance (QA) and Quality Control (QC)"**	Section E on the recommendation that "investigators should ensure that they are aware of QA and QC procedures used by the data holders": A centralized database including the quality evaluations of major e-HC data sets by independent organizations would be valuable to provide unbiased assessments for the Agency and for the investigators to rely on.
Line 464:	"Other designs, including case-cohort or case-crossover design, can be used depending on the study question of interest and what is known about the postulated relationship between drug exposure and the specific safety outcomes of interest."	We suggest revising as follows: "Other designs, including case-cohort self- controlled case series, or case-crossover design, or quasi-randomization methods such as the use of instrumental variables"
Lines 477-479:	"If multiple comparator groups are employed, the primary comparator for statistical purposes should be identified and the protocol should include an explanation of the rationale for the selection of each group with respect to the study questions of interest."	If multiple comparators are to be included, should statistical adjustment be made for the number of comparisons performed? Please clarify.
Lines 486-487:	"If historical comparators are used, it is important to explain the rationale behind their use and to address the associated limitations."	Examples of the limitations of historical controls were provided would be helpful in this section.
Line 496:	"It can also be appropriate to use self-control, or case-crossover designs, where the same person serves as his or her own control (Maclure 145)."	Please revise to: "It can also be appropriate to use self-control, or self-controlled case series/case-crossover designs, where the same person serves as his or her own control."

		Additionally, please add self-controlled case series and reference provided below. Whitaker, H.J., et al., Tutorial in biostatistics: the self-controlled case series method. Stat Med. 2006.25(10):1768-97.
Lines 516-519:	"The suspicion of unidentified or inadequately addressed confounding can threaten the validity of all pharmacoepidemiologic safety studies. Therefore, it is important for investigators to describe the processes used to identify potential confounders and to provide a scientific rationale for the methods selected to handle them."	We believe that the words "The suspicion of" are not required in this sentence. Unidentified or inadequately addressed confounding can indeed of themselves threaten the validity of all pharmacoepidemiologic studies. Please revise to: "~~The suspicion of unidentified or I~~ Inadequately addressed confounding can threaten the validity of all pharmacoepidemiologic safety studies. Additionally, the study report should address potential for both measured and unmeasured confounders. For example, alcohol usage may not be collected. However, one of the adverse events of interest is liver-related death.
Line 522:	"There are multiple epidemiologic and statistical methods, some traditional (e.g., multiple regression) and some innovative (e.g. propensity scores), for identifying and handling confounding."	We note that confounding cannot be identified without subject matter knowledge. Therefore statistical methods should not be used to identify confounding. We suggest deleting "identifying and" "There are multiple epidemiologic and statistical methods, some traditional (e.g., multiple regression) and some innovative (e.g. propensity scores), for ~~identifying and~~ handling confounding."

Lines 525-527:	"FDA encourages the continued development, use, and evaluation of innovative methods for controlling confounding in pharmacoepidemiologic safety studies using electronic healthcare data."	There are many explorative methods related to analysis and study design that can be useful for addressing specific issues related to pharmacoepidemiologic research. It is not entirely clear how acceptable the regulators find these methods for committed studies. Is it possible for FDA to provide a list of examples that are accepted as valid new methods for regulatory committed safety studies? Please include examples of innovative methods that have been accepted by the Agency.
Lines 532-536:	"The score can be used to achieve balance in the distribution of potential confounding factors between the exposed (to the drug of interest) and comparator with respect to the measured covariates (Rosenbaum and Rubin; D'Agostino). ***Diagnostics*** of the propensity score model should be presented to allow for assessment of its performance and fit."	Although the intent of the propensity score approach may be "...to achieve balance in the distribution of potential confounding factors between the exposed (to the drug of interest) and comparator with respect to the measured covariates" an imbalance may exist between the groups, especially in the tails of the distribution. In this case, sensitivity analyses may be required. Also, reliance on propensity score analyses in some situations may be problematic as patients may cycle through medications in an attempt to achieve and subsequently maintain control of their medical condition (e.g., HIV/AIDS).
Lines 540-541:	"Another approach used by some investigators to address confounding is to exclude patients who have risk factors for the outcome that are not related to the exposure of interest."	If risk factors for an outcome are not related to the exposure of interest then they will not tend to confound the association. This related text may possibly fit better with discussion of effect modification. Stratification will permit one to see how associations between exposure and outcome vary across various populations at different levels of risk.
Line 551:	"…age, gender, and race...."	Please revise to "age, gender, race, and ethnicity."
Lines 558-560:	"Confounding by indication might lead to the appearance of an association between a drug and a safety outcome when the association is actually due to the underlying	We question the accuracy of this statement as written. Confounding by indication will lead to a true association between an exposure and an outcome. However, the

	disease or indication for which the drug is prescribed."	association will not represent a true causal effect. Please revise statement to: "Confounding by indication ~~will~~ might lead to ~~a true~~ an association between ~~an exposure and an outcome~~ a drug and a safety outcome that is not due to a causal effect of the drug on the outcome. ~~However, the association will not represent a true causal effect~~"
Lines 571-572:	"Investigators should also indicate how ***time-varying confounders*** and potential unmeasured confounders (e.g., smoking, OTC drug use, or dietary supplement use) are operationally defined or explored."	The Draft Guidance states that potential unmeasured confounders should be operationally defined or explored. This would impose practical difficulties; since variables are unmeasured, investigators would not be able to explore the variables.
Lines 579:	"Sample size requirements and statistical power should be estimated before initiating the study."	We request that the objective of the sample size and power calculation be clarified. On one hand, for studies using e-HC data sets, the investigators have no control of the size of data sets. In addition, it is unlikely for the investigator to have a good estimation on size of the subpopulation in a data set that is appropriate for the objective of a particular study without a deep dive into the data set. On the other hand, the investigator may already have the access to the data set(s), in which case, the "sample size and power" calculation is not really done "before the initiation" of the study.
Line 585:	"The initial power calculations and the validity of underlying assumptions should be revisited at the end of the study in the context of the results, particularly in the case of negative findings."	Please clarify the meaning of revising the initial power calculations "at the end of the study in the context of the results".
Lines 587:	N/A	The evaluation of "effect modification" requires a larger sample size relative to evaluating main effects (exposure-outcome relationships). Please add the following sentence:

		"Sample size should be sufficient to explore effect modification."
Lines 589-591:	**"B. Study Design: Exposure Definition and Ascertainment** *1. Exposure Definition"*	The first section appears to be out of order. It seems more appropriate to first discuss ascertainment of exposure, and then discuss time at risk of an event due to exposure. We suggest moving this to after the sections on ascertainment. We also suggest changing the title of the first section, and perhaps the overall section, to something more consistent with the concept of defining time at risk of exposure rather than definition of exposure.
Lines 596:	"By obtaining information from other sources, such as spontaneous report data, about the postulated exposure risk window, the likelihood of focusing on only relevant periods of exposure can be increased."	Analysis of the exposure-outcome relationship requires consideration of the etiologically relevant period in addition to the induction period. We suggest adding "etiologically relevant period and the induction period," immediately after "exposure risk window," …exposure risk window, etiologically relevant period and the induction period
Lines 598-600:	"For example, if an adverse outcome is known to only occur immediately after initial use of a drug and the exposure definition includes all of the patient's time on a drug, a significant amount of nonrelevant exposure time could be included and could produce biased risk estimates."	We suggest that it would be helpful use prevalence/incidence tables in part address this concern.
Lines 624-632:	"*Exposure Ascertainment — Study Design"*	We suggest adding a statement about a 'new switcher' design to reflect designs more appropriate to second-line therapies.

Line 644:	"For example, patients may be required to purchase the injectable drug in the pharmacy (NDC code) or the provider may purchase the injectable drug for the patient and bill for the drug and its administration ("J" code)."	We note that newly approved drugs may not have a specific code. We ask that FDA please provide clarification on exposure ascertainment for newly approved drugs that don't have a specific code. The feasibility of capturing exposure using non-specific codes should be addressed in the protocol.
Lines 657-659:	"Since patients often do not obtain refills exactly on time, apparent gaps in therapy often exist in electronic healthcare data, and decisions need to be made as to when these gaps are long enough to suggest true interruption of treatment."	How is "true interruption of treatment" defined? Is this intended to include short-term "drug holidays" which may not be captured by the electronic medical record?
Lines: 664	N/A	Please add persistency and adherence for exposure ascertainment: "Persistency, adherence can be considered to summarize drug exposure"
Lines 691-693:	"Without linkage to dispensing systems, it cannot be assumed that the patient actually filled the prescription. It is important for investigators to ensure the validity of EMR prescribing information before using it to define patient drug exposures."	A very important limitation of electronic medical records is that the prescription records do not necessarily reflect the actual filling by patients. However, the validation to ensure patients receiving a prescription actually filled it is unrealistic if there are no linked pharmacy data. Nonetheless, assuming the potential misclassification is nondifferential, prescription data can still be a very useful proxy of received treatment. Please clarify that such validation is valuable but many times impractical.
Line 695:	**"C. Study Design: Outcome Definition and Ascertainment"** The guidance document has gone into quite a bit of detail regarding exposure definition, but less so on outcome definition.	We suggest that the outcome definition should be focused on the incident or recurrent events. Also, please highlight the need for an appropriate "adjudication charter" to ensure such validation steps are appropriately documented.

		Please include text on Incident/Recurrent events, need for adjudication charter – esp. for safety studies focusing on rare events.
Lines 709-711:	"Case definitions for outcomes should be developed independently of drug exposure status, and exposure to the drug should not be an inherent component of the outcome definition."	We request that FDA clarify that this remark applies not just to the question of whether the subject was exposed, but also to the degree of exposure.
Line 714:	N/A	Please add clarification when outcome ascertainment relies on medical chart review: "When outcomes of interest are verified based on medical chart review, the medical chart extraction rate, extraction form, and blinded review process should be considered."
Line 715:	"*2. Validation of Outcomes*"	Although validation is extremely important, consistency of the outcome definition also should be of interest. This is especially true when combining information from several different electronic medical record databases.
Line 722:	"Although this validation is critical for all safety studies, it is especially important for certain vaccine outcomes, as they are often rare events for which coding practices cannot be known or assumed."	We suggest replacing "*Although this validation is critical…*" with a statement closer to "*Although this validation is important…*" since the document then continues (in line 728) "For studies without outcome validation…" "Although this validation is ~~critical~~ important for all safety studies…"
Line 732:	"FDA recommends that outcome definitions be specified and explained *a priori* and incorporate the coding system of the data source(s) used."	It is not clear the value of a priori specification of definitions in situations where the Sponsor may have access to the data sets well before the protocol is created. We recommend that this distinction should be made in this section.

Lines 744:	"Therefore, when using claims data, it is preferable to use and validate inpatient codes when defining outcomes whenever possible because these codes are often more reliable and generally reflect more serious diseases."	Please replace "and validate" with: "~~and validate~~ and comment on the validity of"
Lines 758-759:	"As implementation of EMRs becomes more widespread, investigators will be challenged to develop innovative strategies to confirm electronic exposure and outcome data, and FDA encourages such efforts as they are critical to ensure the validity of studies relying upon these data."	This verbiage suggests that hardcopy medical records are somehow more valid than electronic medical records, which is unsubstantiated. We recommend citing the source of this information or deleting the entire passage.
Line 771:	"Death is a particularly difficult outcome to ascertain reliably using electronic healthcare data."	Please replace "electronic healthcare data." With: "electronic ~~healthcare~~ claims and medical record data." Additionally, please clarify that access to death certificate data is limited for Europe.
Lines 778:	"The use of death certificate data is subject to all the known limitations of such data."	We recommend that this statement should be referenced to provide justification of "all the known limitations". Please include references and examples of the limitations of death certificate information.
Lines 787:	N/A	Record linkage to National Death Index (NDI), while not always feasible due to lack of patient identifiers, should be considered as a strategy if mortality is a study outcome of interest. Please add the following sentence: "Ideally, where death is an important outcome, study design should include consideration of record linkage to NDI."

VI. BEST PRACTICES--ANALYSES		
Lines: 788	**"VI. BEST PRACTICES — ANALYSES"**	As discussed in our general comments, some Sponsors also submit a separate statistical analytical plan in addition to a protocol. In the analytical plan, statistical analyses are specified in greater detail. This approach is particularly helpful for studies involving multiple investigators and data systems as the analysis strategies could not be finalized before a thorough discussion with all investigators which typically happens after the study is approved. Please clarify if it the FDA's intent to have the detailed analysis strategy outlined in protocol?
Line 805:	…"statistically significant results that are inaccurate can easily be found."	The term "misleading" rather than "inaccurate" may be more appropriate here. Please consider revising to: "statistically significant results that are ~~inaccurate~~ misleading can easily be found."
Line 810:	N/A	Please provide the FDA's position on the adjustment for multiple comparisons in the context of an analysis plan for an observational research study.
Line 823:	"The reported results should be stratified by the key effect modifier."	Should "key modifier" be "key modifiers"? We should allow the possibility of more than one.
Line 829-837:	"**D. Sensitivity Analyses"**	Sensitivity analyses should also be performed in the event of missing data. What imputation techniques should be employed (e.g., missing [completely] at random, missing not at random)? We recommend that this should be consistent with, and possibly refer to, other ICH or guidance documents that discuss missing data.
Line 832:	"FDA recommends the use of sensitivity analyses to determine the impact of various study decisions relating to design, exposure definition and outcome definition."	We recommend that this sentence be modified to include other variables that play a key role in analysis (*e.g.*, stratification factors), rather than be limited to just

		exposure and outcome.
Lines 841:	"If applicable, the analysis plan should include information on how data are to be pooled from different sources. If relevant, investigators should also describe how data are linked or standardized to allow for pooling."	While there are many considerations related to the use of multi-database methodology/meta-analysis, which may be the basis of future FDA guidance, we request additional detail and references where available.
Lines 855:	"**G. Quality Assurance (QA) and Quality Control (QC)"**	The heading is not aligned with paragraph information. Please change to "G. Quality Control (QC) and Quality Assurance (QA)"
Lines 869:	"FDA could request access to the original analytic data set to conduct re-analyses of the data to verify study results."	For how long should the analytic data sets be kept? Some data providers require the return or destruction of study data once the study has been completed or following termination of the data licensure contract.
Line 951:	"Pharmacoepidemiologic safety study."	Please clarify if a health outcomes study with safety as a secondary objective would be qualified as a pharmacoepidemiology safety study.
N/A	N/A	We would like to request FDA's perspective on how electronic health records can or cannot be pooled.
N/A	**N/A**	In some cases the topic of the guidance would include studies carried out in non-US data sources. It would be useful to provide some guidance around when safety studies using non-US electronic healthcare datasets would *not* be expected to be shared with the FDA, including specific examples.