



Response to:

US Food and Drug Administration Docket No. FDA – 2009-D-0283

**Guidance for Industry
Postmarketing Studies and Clinical Trials-
Implementation of Section 505 (o) of the
Federal Food, Drug, and Cosmetic Act**

**Submitted by the
International Society for Pharmacoepidemiology**

October 9, 2009

RE: FDA “Guidance for Industry Postmarketing Studies and Clinical Trials — Implementation of Section 505(o) of the Federal Food, Drug, and Cosmetic Act” (FDA-Draft-505 (o)-Guidance-7-16-09).

The International Society for Pharmacoepidemiology (ISPE) is very pleased to have the opportunity to offer our perspectives and suggestions, and submits for your consideration the following comments on the on the FDA “Guidance for Industry Postmarketing Studies and Clinical Trials — Implementation of Section 505(o) of the Federal Food, Drug, and Cosmetic Act” (FDA-Draft-505 (o)-Guidance-7-16-09).

ISPE is an international, nonprofit, professional membership organization dedicated to promoting the health of the public by advancing pharmacoepidemiology, the science that applies epidemiological approaches to studying the use, effectiveness, values and safety of pharmaceuticals. ISPE is firmly committed to providing an unbiased scientific forum to the views of all parties with interests in drug, biologics, and devices development, delivery, use, costs and value, adverse and beneficial effects, and therapeutic risk management.

Moreover, the Society provides an international forum for the open exchange of scientific information among academia, government, and industry and for the development of policy; a provider of education; and an advocate for the fields of pharmacoepidemiology and therapeutic risk management.

The Society’s more than 1,000 members represent 30 countries. ISPE members work in academic institutions, the pharmaceutical industry, government agencies, and non-profit and for-profit private organizations. ISPE members are researchers with background and training in epidemiology, biostatistics, medicine, public health, nursing, pharmacology, pharmacy, law, and health economics.

Our comments are based on a careful review of the FDA Guidance by the Society’s Board of Directors, Executive Committee, and Public Policy Committee.

These are the Society’s consensus comments:

General comments:

One of the main advances of this document is that it differentiates between trials and "studies" as follows: "FDAAA makes a new distinction between “study” and “clinical trial.” Previous laws, regulations, and practice have used the terms studies and trials interchangeably." We appreciate this clarification but would like to see the phrase “randomized trials” used instead of “trials”. The best distinction is between experimental studies (randomized trials) and non-experimental studies.

It would be helpful to clarify the relationship of risk evaluation and mitigation strategy (REMS) assessments and Postmarketing Requirements (PMRs). Under which circumstances, if any, will REMS assessments be considered PMRs?

In addition, it may be helpful to distinguish studies using de novo data collection from those where a database is used. We think the need for de novo data collection will depend on detailed circumstances and it may be sensible not to set out detailed requirements in guidelines but allow for flexibility.

Specific comments:

Section, Lines	Suggestion	Rationale
II B, 99-101	<p>More clearly distinguish between randomized trials and non-experimental studies, and more narrowly define randomized trials contrasting them with investigations where routine clinical care is used entirely.</p> <p>It would also be helpful to clearly define where a study with baseline randomization but purely observational follow-up (i.e. large simple trial) fits into these definitions.</p> <p>**We also suggest that all de novo data collection studies (clinical trials, large simple trials, cohort studies, etc.) have the same periodic reporting requirements.</p>	<p>The current definitions of clinical trials and studies are too vague, leaving room for multiple interpretations. As written, it appears that any required procedure (e.g. a measure of height and weight at regular intervals) would deem a study interventional. De novo non-experimental studies sometimes have required procedures that are part of routine care, borderline routine, or non-routine but non-invasive (e.g. taking yearly height/weight, or conducting yearly FEV1 tests). These should be considered separately from clinical trials, which include randomization and non-routine, or more invasive procedures.</p>
II B, 118-134	<p>For all studies with de novo data collection (e.g. pregnancy registries or other safety registries), we recommend a timetable for completion. Since many of the PMRs/PMCs will be long-term studies, study design factors should be clearly delineated and monitored, and adjustments to the timetable justified.</p>	<p>As with any prospective study, the validity of assumptions that impact estimated sample size, feasibility and duration should be monitored over time).</p>
III A, 191-192	<p>Suggest that the phrase "attributed to" be replaced with "associated with" or be changed to "attributed to <u>or</u> associated with".</p>	<p>Pharmacoepidemiology studies are often used to further understand associations that are not yet demonstrated or accepted as causally related.</p>

<p>III A, 193-195</p>	<p>Sentence beginning with "To facilitate..." It would be helpful to expand somewhat on the idea that pharmacoepidemiologic studies should have a protocol - this is too vague. Also, the second part of the sentence implies that the reason to have a control group is solely to "test prespecified hypotheses". Suggest editing this to sentence to read: "To facilitate interpretation of the findings, the studies should have a protocol that meets accepted standards for good pharmacoepidemiology practices and a control group, unless there is a scientifically valid reason to exclude controls." with reference to the ISPE guidelines for Good Pharmacoepidemiology Practices.</p>	<p>Without prespecified protocol criteria, the quality of study protocols may vary greatly.</p> <p>Control groups are useful even when the stated purpose of the study is for estimation (relative to no treatment or alternative treatment). The exact nature of the control group will be vital in the interpretation but will depend on the particular study.</p>
<p>III A, 207</p>	<p>Suggest editing the pregnancy study example to read "Compare the incidence of adverse fetal/child outcomes after patient drug exposure during pregnancy with that of pregnant patients who did not receive the drug".</p>	<p>The example currently reads as if the study is intended to measure the frequency of pregnancy, not the frequency of pregnancy outcomes among exposed pregnancies.</p>

Again, we thank FDA for allowing us the opportunity to comment on this document. ISPE welcomes any future dialogue on the proposed *Guidance for Industry Postmarketing Studies and Clinical Trials — Implementation of Section 505(o) of the Federal Food, Drug, and Cosmetic Act*" (FDA-Draft-505 (o)-Guidance-7-16-09).

Sincerely,

Public Policy Committee,
International Society for Pharmacoepidemiology (ISPE)