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April 21, 2008

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2008-D00053, Draft Guidance for Industry on Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices

Dear Sir/Madam:

The American Society of Health-System Pharmacists (ASHP) is pleased to submit written comments pertaining to the Draft Guidance for Industry on Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices (draft guidance). The Society's more than 30,000 members include pharmacists and pharmacy technicians who practice in a variety of health-system settings, including inpatient, outpatient, home care, and long-term-care settings.

ASHP appreciates the agency's willingness to provide its current views on the dissemination of medical journal articles relating to unapproved uses of approved drugs. ASHP recognizes the need for unlabeled uses of approved medical products. The ASHP Statement on the Use of Medications for Unlabeled Uses states: "The prescribing, dispensing, and administration of FDA-approved drugs for uses, treatment regimens, or patient populations that are not reflected in FDA-approved product labeling often represent a therapeutic approach that has been extensively studied and reported in medical literature. Such uses are *not* indicative of inappropriate usage. Health care professionals should appreciate the critical need for freedom in making drug therapy decisions and understand the implications of unlabeled uses."

Good medical practice and the best interests of the patient require that clinicians use legally available drugs, biologics, and devices according to their best knowledge and judgment. If clinicians use a product for an indication not in the approved labeling, they have the responsibility to be well-informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects.¹

Furthermore, federal legislation recognizes that primary literature should supplement existing mechanisms for assessing medical acceptance of off-label uses. Under Medicare Part B (Section 1861(t)(2)(B)(ii)(II) of the Social Security Act), the term “medically accepted indication” includes a use of a drug other than the use for which it has been approved by the FDA if the use is supported by one of the listed compendia *or* “the carrier involved determines... that such use is medically accepted based on supportive clinical evidence in peer reviewed medical literature appearing in publications which have been identified for purposes of this sub clause by the Secretary.”

While ASHP recognizes the need for and supports the unlabeled use of approved medical products, the Society does not view the dissemination of materials by pharmaceutical industry representatives as an effective and appropriate means of educating health care providers regarding off-label uses of drugs and biologics. ASHP acknowledges that the distribution of these materials may help to increase awareness of important, well-conducted clinical trials. However, given the increased availability of on-line information, the Society believes that the primary motivation behind the pharmaceutical industry’s distribution of these materials is likely to be promotional rather than educational.

Consequences of Widespread, Inappropriate Off-label Uses

ASHP is concerned about the potential consequences of the widespread, off-label use of a drug in response to unsolicited, industry-distributed promotional materials containing information about indications and patient populations outside of the FDA product labeling. As stated previously, ASHP recognizes that it is acceptable medical practice to prescribe drugs for off-label uses, including, in some cases, a modified regimen. In many cases, this practice is considered low-risk, especially when used for a single patient after thoughtful consideration of risk/benefit concerns.

However, the off-label use of a drug may be systematically expanded into a broader group of patients, including the use of alternative regimens not supported by a clinical trial, and without the lack of oversight by an authoritative body (i.e., an Institutional Review Board or the FDA). This practice may be considered high-risk due to the

¹ FDA Information Sheet for Institutional Review Boards (IRB): Off-label and investigational use of marketed drugs, biologics, and medical devices. Guidance for Institutional Review Boards and Clinical Investigators. 1998 Update.

potential exposure of a large number of patients who may be at greater risk for side effects, drug-drug interactions, or ineffective therapy.

ASHP is also concerned that, if an off-label use becomes widely accepted or endorsed by the medical community, manufacturers may be less inclined to conduct formal, controlled comparative trials, and therefore important information about toxicity and efficacy in other patient populations may not be fully established.

The optimal method for educating health care providers about off-label uses of drugs and biologics is through the publication of information contained in a well-designed, controlled, balanced, and unbiased clinical trial, published in a peer-reviewed biomedical journal. Continuing education programs provided by professional organizations, in which the clinical content is not influenced by a for-profit company, provide the best educational opportunity for health-care providers to learn about an off-label use. Through these education programs, proper patient selection criteria and patient safety issues can be presented in a well-balanced and clinically relevant manner without concerns about the integrity of the clinical information or the perception of bias or promotion.

Quality of Reprints, Articles, and Reference Publications

ASHP is concerned by changes in the draft guidance to the previous statutory requirement relating to the pre-approval review process for the release of materials containing off-label uses, and also by the removal of the requirement that distributed materials relating to off-label uses be part of a formal clinical investigation intended for submission as part of a supplemental new-drug application (sNDA).² Given the lack of a prospective review process to ensure that information contained in a reprint or article is high-quality, balanced, and adequately comprehensive to address risk-benefit considerations, ASHP recommends that the FDA expand its requirements to address the quality of the publications intended for dissemination by representatives of the pharmaceutical industry.

There are several recent cases of inappropriate practices of pharmaceutical manufacturers that signal the need for a more stringent approach and closer oversight by FDA than what is proposed in the draft guidance. The case studies on rofecoxib in the April 16, 2008 issue of *JAMA* are a chilling accounting of the extent to which some manufacturers may compromise ethical practices in research design and journal publication. The draft guidance would be unlikely to prevent these practices.

² A clinical investigation is defined by the FDA as “any experiment that involves a test article and one or more human subjects that either is subject to requirements for prior submission to the FDA, or is not subject to requirements for prior submission to the FDA under the sections of the Federal FDC Act, but the results of which are intended to be submitted later to, or held for inspection by the FDA as part of an application for a research or marketing permit.” Test articles that are subject to regulation under the Federal FDC Act include all drugs, including a biologic product for human use, and medical devices.

While ASHP believes that FDA should reinstitute a requirement for formal FDA review and approval of journal articles describing off-label uses distributed by manufacturers, the Society recognizes that FDA may not reinstitute such a requirement at this time. Therefore, ASHP recommends that, under the draft guidance, FDA require the distribution of comprehensive information that identifies and selects clinical trials that closely fulfill the requirements of a formal clinical investigation.

Alternatively, the International Committee of Medical Journal Editors (ICMJE) requires registration of a clinical trial onto a public clinical trial registry (e.g., clinicaltrials.gov) as a prerequisite for possible publication in one their biomedical journals. The ICMJE states that all phase III clinically-directed trials in which a concurrent control or comparison treatment is prospectively assigned must be registered prior to patient enrollment.³ Additionally, the FDA requires that all studies involving serious or life-threatening conditions, regardless of study design or objectives, must also be registered on the National Library of Medicine's clinical trials registry (clinicaltrials.gov). Therefore, to provide some assurance of high standards, ASHP recommends only the dissemination of published studies that have been identified as being registered on a public international clinical trial registry.

ASHP was pleased to see FDA's proposed requirement that a journal article distributed under this draft guidance should be published by an organization that has an editorial board of experts, uses a peer-review process, and has a publicly stated policy of full disclosure of any conflict of interest for all authors.

ASHP recommends that FDA include the following additional requirements in its draft guidance:

Any journal article that is distributed to support an off-label use should contain evidence derived from:

- A comprehensive clinical trial with clearly defined inclusion and exclusion criteria describing the patient population(s), discussions about risk-benefit considerations, a complete description of toxicities, and a study that is conducted using high-methodologic principles; and
- A comprehensive clinical trial with a defined comparator treatment arm (i.e., an acceptable existing treatment). The use of studies containing placebo arms or regimens that the medical community views as substandard (either by drug selection or inferior dose) are not desirable given the potential for exaggeration of clinical results.

³*Is this clinical trial fully registered?* A statement from the International Committee of Medical Journal Editors (ICMJE), May 2005.

- Where the study is sponsored by a for-profit company, the reprint must fully disclose the roles of the employees of the company regarding data collection, monitoring of data, and authorship. ASHP believes that published studies in which these activities can be primarily or solely attributed to the academic investigators involved with the study, as outlined in the recent commentary published in the Journal of American Medical Association (JAMA),⁴ represent the most balanced and unbiased conduct and publication of a clinical trial.

In the draft guidance, FDA lists examples of publications that would not be considered consistent with good reprint practices. ASHP recommends adding reports of Phase II trials and clinical narratives to this list. Language in the draft guidance states that a bibliography or lists of references must accompany any material containing an off-label use. The Society recommends that an explicit requirement be made to provide a bibliography containing all published studies for a given drug used for a similar off-label use, including those containing negative or equivocal findings.

ASHP appreciates this opportunity to present its written comments on the draft guidance. Please feel free to contact me if you have any questions regarding comments provided on behalf of ASHP. I can be reached by telephone at 301-664-8702, or by e-mail at jcoffey@ashp.org.

Sincerely,



Justine Coffey, JD, LLM
Director, Federal Regulatory Affairs

⁴ DeAngelis CD and Fontanarosa PB. Impugning the integrity of medical science: the adverse effects of industry influence. JAMA. 2008; 299; 1833.