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# Consumer Federation of America

July 23, 1998

Dockets Management Branch (HFA-305)  
Food and Drug Administration  
12420 Parklawn Drive, rm. 1-23  
Rockville, MD 20857

## **Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices; Docket No. 98 N-0222**

To Whom It May Concern:

The Consumer Federation of America urges the Food and Drug Administration to enact strong regulations governing the dissemination of information related to unapproved and new uses of marketed drugs, biologics and devices. The adoption of the off-label provisions followed a negotiated compromise which included a system of "safeguards". The insertion of the sunset provision is proof of the controversy. There is virtually no legislative history, and the statute language is prescriptive, leaving little to FDA interpretation. In general, we think the FDA has acted correctly here to protect public health and safety.

CFA opposed last year's Food and Drug Administration Modernization Act (FDAMA). Among other concerns, we were distressed by the lowering of the efficacy standard and the adoption of Sec. 401 [codified as Sec. 551], allowing off-label promotion. Separately and together, we believe they will allow millions of Americans to use products whose safety and effectiveness has not been thoroughly established.

CFA is also a signatory to comments in this Docket filed with other patient and consumer organizations. Those comments are incorporated herein by reference. We offer the following additional comments.

### Information that may be disseminated Sec 99.101

First, the definition of "scientifically sound" is within the FDA's discretion, subject to an "arbitrary or capricious" standard. It is important that the FDA give unambiguous direction to industry, as it has done so here.

More to the point, based on our discussions with experts, what the FDA is requiring here is nothing more than the standard format for articles in peer-reviewed literature. The attached page from the Journal of the American Medical Association's Instructions to Authors bears this out.

Further, the medical journal editor who spoke at the public hearing did not indicate concern about the proposed definition, but welcomed clear guidance from the FDA. With the passage of FDAMA, we are entering a new paradigm in drug testing and marketing. Is there any doubt that there will be increased incentive get the results of clinical investigations published quickly? To the extent that journals on the Index Medicus do not require such disclosures in articles, they should.

At least in the case of health care practitioners, this information needs to be included in the article for a fair evaluation. Under the usual time constraints, it is both unrealistic and unfair to expect a practitioner to independently track it down.

#### Mandatory statements and information Sec. 99.103

There is little opportunity for FDA interpretation here.

The factors listed for consideration in determining whether a statement is "prominently displayed" do not dictate a particular format, but serve notice that valuable information cannot be buried or downplayed by clever packaging.

There should be no confusion about what is required of manufacturers. More important, recipients of the information should not be confused. This can best be accomplished by an up-front, consistent [in terms of wording] notice of the off-label nature of the use being promoted.

#### Economically prohibitive supplements Sec 99.205

It is up to the FDA to define "economically prohibitive". It must give consistent and clear construction while not allowing the exceptions to become the rule. This is an area fraught with controversy. What does it really cost to conduct studies?

We believe that the FDA has given a fair construction of the word "prohibitive". After all, Congress did not say economically "difficult" or "practical". Given the indefinite nature of this exemption, it should only be used in the rarest of circumstances.

CFA supports requiring the report of an independent certified public accountant

instead of manufacturer attestation. This will ensure some level of due diligence in reviewing cost estimates and, presumably, less pressure to inflate the numbers.

#### Manufacturer statements and certifications

In several sections [99.201, 99.203, 99.205, 99.303], the manufacturer is required to submit a statement or other documents to the FDA. CFA recommends that all such statements, certifications and documents be certified by an officer from the manufacturer's executive committee.

The risks associated with off-label dissemination are great, and we expect high public scrutiny. Senior management must be vested in the process and must not be able to evade public responsibility downstream.

#### Recordkeeping and reports

CFA urges that in ALL cases, manufacturers be required to keep records identifying individual recipients of the disseminated information. Short of that, there is no guarantee that timely and decisive corrective action can be taken in the event of a serious adverse effect. Cessation of dissemination is not the critical issue, it is notification of those already at risk. Without the ability to notify practitioners, there is less chance of success.

Presumably, off-label dissemination is not meant to circumvent FDA review and should be limited in scope. Therefore, any recordkeeping burden is outweighed, at least in the short term, by the risk presented and the need to make off-label dissemination work safely.

#### Request for clarification

Finally, we seek clarification under Sees 99.201 (a) and 99.501 (b)(3) that a manufacturer must submit any additional article or publication to the FDA for 60-day review before it can be disseminated. While we think it clear from 99.201, that this is the case, there should be no room for argument under section 99.501 that making the semiannual filing is sufficient once the manufacturer has received the initial approval to disseminate information about a particular use.

Respectfully submitted,



Mary Rouleau  
Legislative Director

# JAMA Instructions for Authors

## MANUSCRIPT CRITERIA AND INFORMATION

*JAMA* is an international, peer-reviewed, general medical journal, with simultaneous printing in the United States and United Kingdom, distribution to readers in more than 148 countries, and 18 separate international editions published in 11 languages.

**Manuscript Submission.**—All manuscripts should be sent to the Editor, George D. Lundberg, MD, *JAMA*, 515 N State St, Chicago, IL 60610 USA; telephone: (312) 464-2402; fax: (312) 464-5824; e-mail: JAMAms@ama-assn.org.

Manuscripts are considered with the understanding that they have not been published previously in print or electronic format and are not under consideration by another publication or electronic medium. A complete report following presentation at a meeting or publication or preliminary findings elsewhere (eg, in an abstract) can be considered. Include copies of possibly duplicative material that has been previously published or is currently being considered elsewhere. Authors submitting manuscript or letters to the editor regarding adverse drug or medical device reactions, reportable diseases, and the like should also report such to the relevant government agency.

**Electronic Submission.**—Short manuscripts that do not contain tables or figures and letters to the editor may be submitted via e-mail. Send letters to JAMA-letters@ama-assn.org (see instructions below). Send short manuscripts to JAMAms@ama-assn.org. All manuscripts sent via e-mail must be copied and embedded in the actual e-mail message. Do not send attachments.

### categories of Articles

*JAMA* publishes original contributions, review articles, brief reports, special communications, commentaries, letters to the editor, and many other categories of articles. Topics of interest include all subjects that relate to the practice of medicine and the betterment of public health worldwide. The most frequent categories of articles are described below.

**Original Contributions.**—Randomized controlled trials (see page 71 for specific instructions), intervention studies, studies of screening and diagnostic tests, outcome studies, cost-effectiveness analyses, case-control series, and surveys with high response rates. Registered trials should include the registry and registration number. Each manuscript should clearly state an objective or hypothesis; the design and methods (including the study setting and time period, patients or participants with inclusion and exclusion criteria, or data sources and how these were selected for the study); the essential features of any interventions; the main outcome measures; the main results of the study; a comment section placing the results in the context of published literature; and the conclusions. For more information, see Instructions for Preparing Structured Abstracts on page 71. Typical length: 2000-4000 words (not including tables, figures, and references).

**Reviews.**—Systematic, critical assessment of literature and data sources pertaining to clinical topics, emphasizing factors such as cause, diagnosis, prognosis, therapy, or prevention. All articles and data sources reviewed should include information about the specific type of study or analysis, population, intervention, exposure, and tests or outcomes. All articles or data sources should be selected systematically for inclusion in the review and critically evaluated, and the selection process should be described in the paper. Meta-analyses also will be considered as reviews. Review manuscripts that do not meet these criteria will not be accepted. For more information, see Instructions for Preparing structured Abstracts on page 71. Typical length: 4000 words (not including tables, figures, and references).

**Brief Reports.**—Short reports of original studies or evaluations. We will also consider clinical cases (individual or a series), but they must be unique, first-time reports. Individual case reports are rarely accepted for publication. Typical length: 750-1500 words (not including tables, figures, and references).

**Letters to the Editor.**—Letters discussing a recent *JAMA* article are welcome. They should be received within 4 weeks of the article's publication and can be faxed to the editorial office in Chicago at (312) 464-824 or sent via e-mail to JAMA-letters@ama-assn.org. For faxed letters, please also send a hard copy by surface mail. Letters reporting original research including case series or case reports, also are welcome. Letters should be typewritten, double-spaced, and must not exceed 500 words of text and 5 references.

## Criteria for Manuscript Acceptance

Manuscripts submitted to *THE JOURNAL* should meet the following criteria: the material is original; the writing is clear; the study methods are appropriate; the data are valid; the conclusions are reasonable and supported by the data; the information is important; and the topic has general medical interest. From these basic criteria, we assess a paper's eligibility for publication. We receive approximately 4000 papers each year, but publish only about 11% of unsolicited manuscripts. Because of this competition for space in *THE JOURNAL*, we advise authors to follow these instructions and to keep papers as brief as possible while still meeting the quality criteria described herein.

### Authorship Information

Designate a corresponding author and provide a complete address, telephone and fax numbers, and e-mail address. Authors may include explanation of each author's contribution and add a publishable footnote explaining specific contributions.

**Group Authorship.**—If authorship is attributed to a group (either solely or in addition to 1 or more individual authors), all members of the group must meet the full criteria requirements for authorship described in the following paragraphs. A group may designate 1 or more authors to take responsibility "for" the group, in which case the other group members are not authors, but may be listed in an acknowledgment.

**Authorship Requirements.**—With the cover letter include (1) the statement on authorship criteria and responsibility and (2) the statement on financial disclosure and (3) either the statement on copyright or the statement on federal employment. Each of these 3 statements must be read and signed by all authors. (4) The corresponding author must sign the Acknowledgment statement. (See also page 69.)

**1. Authorship Criteria and Responsibility.**—All persons listed as authors must meet all the following criteria for authorship: "I certify that I have participated sufficiently in the work to take public responsibility for the content.

• I certify that (1) I have made substantial contributions to the conception and design or analysis and interpretation of data; and (2) I have made substantial contributions to drafting the article or revising it critically for important intellectual content; and (3) I have given final approval of the version of the article to be published.

• I certify that the manuscript represents valid work and that neither this manuscript nor one with substantially similar content under my authorship has been published or is being considered for publication elsewhere, except as described in an attachment.

• I attest that, if requested by the editors, I will provide the data or will cooperate fully in obtaining and providing the data on which the manuscript is based for examination by the editors or their assignees."

(Continued on next page.)

### Manuscript Checklist

- 1. Include original manuscript and 3 photocopies.
- 2. On the title page, include a word count for text only, exclusive of title, abstract, references, tables, and figure legends.
- 3. Include statements—signed by each author—on (1) authorship criteria and responsibility, (2) financial disclosure, and (3) copyright transfer or federal employment.
- 4. Include statement signed by corresponding author that written permission has been obtained from all persons named in the Acknowledgment.
- 5. Include research or project support/funding in an Acknowledgment.
- 6. Double-space manuscript (text and references) and leave right margins unjustified (ragged).
- 7. Check all references for accuracy and completeness. Put references in proper format in numerical order, making sure each is listed in therein.
- 8. Send 4 sets of all illustrations.
- 9. Provide an abstract that conforms with the required abstract format.
- 10. Include written permission from each individual identified as a source for personal communication.
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