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Presentation at the Food and Drug Administration's November 9-10, 2016 Public Hearing on Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products

Michael A. Carome, M.D.
Director, Health Research Group, Public Citizen

In its January 2009 guidance for industry on good reprint practices[1] and its more expansive February 2014 draft guidance on distributing scientific and medical publications on unapproved new uses,[2] the Food and Drug Administration (FDA) articulated "safe harbor" policies that permit pharmaceutical and medical device manufacturers to disseminate scientific and medical journal articles and other materials describing unapproved uses of approved or cleared medical products, provided certain conditions are met.

Both documents state that, if manufacturers distribute scientific or medical publications—such as peer-reviewed journal articles—or other information as recommended in the guidance, the FDA does not intend to use such distribution as evidence of the manufacturer's "intent that the product be used for an unapproved new use." However, the primary purpose for drug and device company representatives to distribute scientific and medical information regarding unapproved uses undoubtedly is to promote those uses to physicians and other health care providers and thereby increase prescribing of the companies' products. For the FDA or anyone else to suggest otherwise defies common sense. Such legalized off-label promotion—even under the safe-harbor conditions specified in FDA guidance—threatens the U.S. regulatory process for ensuring that prescription drugs and medical devices are safe and effective for their intended uses.

The existing legal restrictions on marketing drugs and devices for unapproved uses reflect the fact that assurances by manufacturers that claims of safety and effectiveness are well-supported are no substitute for the FDA's rigorous, independent evaluation of the evidence. As Avorn and colleagues aptly explained in their 2015 *New England Journal of Medicine* article, "physicians and patients could not be expected to determine whether a given drug was safe and

[1] Food and Drug Administration. 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: Guidance for industry. January 2009. http://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm. Accessed October 28, 2016.

[2] Food and Drug Administration. Revised draft guidance for industry: Distributing scientific and medical publications on unapproved new uses — recommended practices. February 2014. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm387652.pdf. Accessed October 28, 2016.

effective without having the benefit of the lengthy and complex evaluation process conducted by FDA scientists and its outside advisors, who assess reams of complex data on pharmacology and clinical trial results, not all of which are publicly available."[3]

Problems With Peer-Reviewed Journal Articles

Peer-reviewed scientific and medical journals vary significantly in their credibility and rigor. But even among the most respected journals, the peer-review process suffers from shortcomings that can permit fraudulent or otherwise misleading articles to find their way into publication. Unlike the rigorous FDA review process for drugs and high-risk medical devices, the peer-review process for scientific and medical journals generally is not well equipped to uncover the wide range of problems that can undermine the integrity of clinical trial data, including outright fraud, flawed study design, failure to adhere to protocol-specified procedures, poorly conducted statistical analyses, and incomplete reporting of key data. Conflicts of interest resulting from financial relationships between authors of peer-reviewed journal articles and manufacturers can increase the likelihood of such problems. And most busy physicians and other health care providers are even less equipped than journal peer reviewers to assess the validity and reliability of data presented in journal articles distributed by manufacturers.

Relying on articles published in peer-reviewed journals, without digging deeper into the underlying data—as occurs when FDA scientists review new drug applications, medical device premarket approval applications, and some 510(k) device premarket clearance applications—can lead to the rapid adoption of ineffective or unsafe unapproved uses of drugs and medical devices, and thus put patients in harm's way.

Research Fraud and Misconduct

Research fraud and misconduct represent the most serious threat to the integrity of data presented in journal articles. The FDA itself has noted that fraud and misconduct have occurred in all phases of clinical research and have involved enrolling unqualified subjects, backdating information, fabricating data from tests that were not performed, failing to report adverse events, deviating from protocols, covering up mistakes, and submitting false data for publication.[4]

Evidence suggests that the incidence of detected research fraud and misconduct, although very low, has increased significantly. For example, a 2012 study of the PubMed database found that the percentage of scientific articles retracted due to fraud had increased approximately tenfold since 1975.[5] Fraud or suspected fraud was the most commonly identified reason for

[3] Avorn J, Sarpatwari A, Kesselheim AS. Forbidden and Permitted Statements about Medications — Loosening the Rules. *N Engl J Med*. 2015;373(10):967-973.
[4] Hamrell MR. Raising suspicions with the Food and Drug Administration: Detecting misconduct. *Sci Eng Ethics*. 2010;16(4):967-704.
[5] Fang FC, Steen RG, Casadevall A. Misconduct accounts for the majority of retracted scientific publications. *PNAS*. 2012; 109(42):17028-17033. (Correction: *PNAS*. 2013;110(3):1137.)

retraction of an article, occurring in 43 percent of cases. The study authors noted that "the current number of articles retracted because of fraud represents an underestimation of the actual number of fraudulent articles in the literature."

Biased Study Design

Far more widespread than outright research fraud, but equally insidious, are a wide range of practices that result in clinical trial bias. In a 2015 editorial in the *Mayo Clinic Proceedings*, Prasad and Berger coined the term "hard-wire bias" to describe sources of potential bias originating in the initial design of randomized, double-blind clinical trials.[6] They pointed out that hard-wire bias cannot be corrected by using statistical methods or reanalysis. Examples described by the authors include selection bias and unequal-comparison bias.

Selection bias can occur when inclusion and exclusion criteria result in a very narrowly defined subject population, which prevents the generalizability of the results to a broader patient population, even though results of clinical trials are routinely used to justify use of the drug in broader populations.[7]

Unequal-comparison bias stems from designs that disadvantage one trial group relative to another, such as selecting an active comparator for the control group that is not consistent with standard-of-care treatment.

Publication bias

Another well-documented problem adversely affecting the scientific and medical literature is publication bias, which is the tendency for investigators to submit manuscripts, and the tendency of editors and reviewers to accept them, based on the direction and strength of the research findings. A 2009 systematic review by the Cochrane Library of studies assessing publication bias found that that clinical trials with positive findings had nearly four times the odds of being published compared to trials with negative findings.[8] Furthermore, trials with positive findings tended to be published sooner—after four to five years—compared to those with negative findings, which were published after six to eight years.

Selective Reporting

Another pervasive problem with peer-reviewed literature is the practice of selectively reporting study findings that are most favorable for medical products. For example, studies

[6] Prasad V, Berger V. Hard-wired bias: How even double-blind, randomized controlled trials can be skewed from the start. *Mayo Clin Proc*. 2015;90(9):1171-1175.
[7] *Ibid*.
[8] Hopewell S, Loudon K, Clarke MJ, et al. Publication bias in clinical trials due to statistical significance or direction of trial results. *Cochrane Database of Systematic Reviews*. 2009, Issue 1. Art. No.: MR000006. DOI:10.1002/14651858.MR000006.pub3.

comparing information in documents submitted to the FDA for drug[9,10] or high-risk medical device[11] approval versus information reported in peer-reviewed medical journal articles have revealed frequent discrepancies in identified primary endpoints and primary study results.

The FDA itself, in its 2010 Transparency Task Force report, noted, "Selective publication of clinical trials results has, in the past, created a misleading picture of the safety and efficacy of a product, with negative implications for the public health. This is particularly pronounced when the product is used off-label."[12]

Finally, extensive evidence shows that companies successfully exploit marketing and promotional techniques to deceive doctors about the safety and effectiveness of drugs and devices for unapproved uses. For example, when selecting educational material to send to doctors or to present at seminars, manufacturers choose material that plays up positive results and omits information about side effects, adverse reactions, and warnings.[13,14]

Conclusions

Given the wide range of problems that commonly undermine the integrity of clinical trial data reported in peer-reviewed scientific and medical journal articles, the FDA's existing January 2009 guidance for industry on good reprint practices permitting promotion of medical products for unapproved uses already undermines the U.S. regulatory process for ensuring that prescription drugs and medical devices are safe and effective for their intended uses and poses substantial risk of harm to patients. Much tighter limits on such communications are essential to protect patients and public health.

[9] Rising K, Bacchetti P, Bero L. Reporting bias in drug trials submitted to the Food and Drug Administration: Review of publication and presentation. *PLoS Med*. 2008;5(11): e217. doi:10.1371/journal. pmed.0050217. (Correction: *PLoS Med* 6(1): e1000017. doi:10.1371/journal.pmed.1000017)

[10] Turner EH, Knoepflmacher D, Shapley L. Publication bias in antipsychotic trials: An analysis of efficacy comparing the published literature to the US Food and Drug Administration database. *PLoS Med*. 2012; 9(3): e1001189. doi:10.1371/journal.pmed.1001189.

[11] Chang L, Dhruva SS, Chu J, et al. Selective reporting in trials of high risk cardiovascular devices: Cross sectional comparison between premarket approval summaries and published reports. *BMJ*. 2015 June 10;350:h2613.

[12] Food and Drug Administration Transparency Task Force. *FDA Transparency Initiative: Draft Proposals for Public Comment Regarding Disclosure Policies of the U.S. Food and Drug Administration*. May 2010. http://www.fda.gov/downloads/AboutFDA/Transparency/PublicDisclosure/GlossaryofAcronymsandAbbreviations/UCM212110.pdf. Accessed November 6, 2016. Page 49.

[13] Washington Legal Foundation v. Friedman, 13 F. Supp. 2d 51 (D.D.C. 1998), vacated on other grounds, 202 F.3d 331 (D.C. Cir. 2000).

[14] Ford M. Another use of OxyContin: The case for enhancing liability for off-label drug marketing. *BU L Rev*. 2003;83:429-464.