June 5, 2017

Dear Members of the U.S. House of Representatives' Energy and Commerce Committee:

The undersigned groups respectfully urge you to oppose H.R. 1703 (the Medical Product Communications Act of 2017) and H.R. 2026 (the Pharmaceutical Information Exchange Act) —and any similar proposals—when your committee convenes to consider legislation that would reauthorize the Food and Drug Administration's (FDA's) user fee programs.

H.R. 1703 and H.R. 2026 together would significantly expand marketing for unapproved uses of drugs and medical devices that have been approved or cleared by the FDA for at least one use. These bills would threaten patient health and safety by undermining the current regulatory regimes for ensuring that drugs and medical devices are safe and effective for each intended use. Similar legislation was considered by Congress during the drafting of the 21st Century Cures Act but was wisely rejected because of its controversial nature.

As the FDA recently articulated, the existing regulatory restrictions on manufacturer communications regarding unapproved uses of approved or cleared medical products are overwhelmingly justified by the substantial government interest in protecting patient health and safety. These restrictions advance health and safety by:

- motivating the development of robust scientific data on safety and effectiveness for each new use of a medical product;
- maintaining the premarket review process for safety and effectiveness of each intended use in order to prevent harm; protect against fraud, misrepresentation, and bias; and prevent the diversion of health care resources to ineffective treatments;
- ensuring that required product labeling is accurate and informative;
- protecting the integrity and reliability of promotional information regarding medical product uses;
- protecting human subjects who are receiving experimental treatments, ensuring informed consent, and maintaining incentives for clinical trial participation;
- protecting innovation incentives, including statutory grants of exclusivity; and
- promoting the development of products for underserved patients.[1]

Together, these interests support the FDA's overarching mission of protecting and promoting public health. That interest outweighs any purported public health benefit of allowing manufacturer communications regarding unapproved uses of medical products.

Dangers of Promotion for Unapproved Uses

Although the FDA approves new drugs and some medical devices before they are marketed, it—and the public—maintains a strong interest in evaluating the products' safety and effectiveness for any additional uses that were not evaluated at the time of initial approval. For example, a drug that poses a serious risk to the patient's immune system may merit approval to treat cancer but not to treat a headache. Thus, the FDA does not evaluate safety in a vacuum: For each

[1] FDA. Memorandum: Public health interests and first amendment considerations related to manufacturer communications regarding unapproved uses of approved or cleared medical products. January 2017. Available at https://www.regulations.gov/contentStreamer?documentId=FDA-2016-N-1149-0040&attachmentNumber=1&contentType=pdf. Accessed May 30, 2017. At 3-16.

proposed use, the agency balances the drug's risk of harm against its potential for benefit. Furthermore, the government has a powerful interest in ensuring that a drug is not only safe for each use for which a manufacturer markets it, but also effective. Marketing for a safe but ineffective use can have detrimental health effects if it diverts patients from effective treatment.[2]

Moreover, a drug's safety for a second use is not established once a drug has been approved (and thus deemed safe and effective) for a first use. To the contrary, a drug that is safe for one use can be life-threatening for another.

Although prescribing drugs and devices for unapproved uses is common, scientific evidence supporting most such uses often is lacking. For example, a recent study conducted in Canada found that the vast majority of off-label uses—81 percent—lacked strong scientific evidence of effectiveness.[3] Patients who received a prescription for an off-label use lacking strong evidence of effectiveness were 54 percent more likely to experience an adverse drug reaction that resulted in stopping use of the drug than were those who were prescribed a drug for an approved use. The increased risk of serious adverse events when drugs are prescribed for off-label uses, combined with the lack of strong evidence of benefit, demonstrates that a favorable risk–benefit relationship has not been established for most off-label uses of drugs and further supports strong restrictions against promotion of unapproved uses.

Even Relying on Peer-Reviewed Scientific Journal Articles is Dangerous

H.R. 1703 is particularly troubling because it would allow pharmaceutical and medical device manufacturers to disseminate a broad range of information related to unapproved uses in both the scientific and lay media. In this way, the bill would radically extend the types of information that can be disseminated by manufacturers beyond what is currently permitted under the FDA's January 2009 guidance for industry on good reprint practices[4] and its more expansive February 2014 draft guidance on distributing scientific and medical publications concerning unapproved new uses.[5]

It is important to recognize that the FDA's current policy of allowing distribution of peer-reviewed journal articles about unapproved uses already allows companies to market drugs based on unreliable and in some cases deceptive evidence of safety and effectiveness. First, published peer-reviewed articles represent a partial, and often biased, sample of all medical evidence regarding the safety and effectiveness of medical products. For example, a 2008 study of antidepressant drug clinical trials submitted to the FDA found that 97 percent of all trials with

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[2] *Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 69 (D.D.C. 1998) (noting evidence that off-label use of calcium channel blockers deprived patients of more effective treatments).

[3] Eguale T, Buckeridge DL, Verma A, et al. Association of off-label drug use and adverse drug events in an adult population. *JAMA Intern Med*. 2016;176(1):55-63.

[4] FDA. 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 May 30, 2017.

[5] FDA. Revised draft guidance for industry: Distributing scientific and medical publications on unapproved new uses—recommended practices. Feb 2014. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm387652.pdf. Accessed May 30, 2017.

positive results had been published, but only 39 percent of the trials deemed by the FDA to have negative or "questionable" results had been published.[6]

Second, 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 and then, via drug salespeople, into doctors' hands. 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 that are distributed by manufacturers.

To underscore the limitations of relying on peer-reviewed scientific and medical journals, the FDA recently explained the following:

> Although some of the assurances from independent review for a particular study can be obtained by review by non-governmental entities (such as peer review coordinated by a scientific or medical journal), the standards governing FDA review provide an assurance of data completeness, scientific rigor, and a thoroughness of evaluation that are not met by the more narrow examination of the peer review process, given the limited data typically available to and reviewed by peer reviewers, the more limited number of peer reviewers (and thus more limited areas of expertise), and the scope of a journal article.[7]

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 pre-market approval applications, and some 510(k) device pre-market 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. And reliance on other types of "scientific" information, such as letters to the editor and information published in the lay media, would be even more dangerous.

Conclusion

History shows that after-the-fact enforcement of safety and efficacy standards for marketing of drugs and devices is inadequate to protect patient safety. Rather, when an unproven assertion of safety and effectiveness is relied on to market a medical product, the resulting harm may be severe—even life-threatening.

[6] Turner EH, Matthews AM, Linardatos E, et al. Selective publication of antidepressant trials and its influence on apparent efficacy. *N Engl J Med*. 2008;358(3):252-260.
[7] FDA Memorandum, supra note 1, at 9.

We urge you to oppose H.R. 1703 and H.R. 2026 and any similar controversial legislation that is introduced in the future. Thank you for considering our views on this important matter.

Sincerely,

Public Citizen
Annie Appleseed Project
Association for Medical Ethics
Breast Cancer Action
Breast Cancer Consortium
Citizens Commission on Human Rights
Doctors for America
Health Global Access Project
Jacob's Institute of Women's Health
National Center for Health Research
The Society for Patient Centered Orthopedics
The TMJ Association
Treatment Action Group