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**The Public Health Risks of Expanding Off-Label Promotion
of Prescription Drugs and Devices**

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Committee on Energy and Commerce
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Summary

- The Guthrie and Griffith discussion drafts dangerously expand the permitted range of off-label statements for manufacturers. Current rules restricting off-label promotion exist because of major public health problems that have arisen from lack of regulation of manufacturer promotional activities.
- Expanding the range of off-label communications will expose patients to drugs that may not work or for which the safety has not been adequately established, and potentially divert use from drugs that we know have benefits that outweigh their risks because they have passed FDA review. It will also increase health care costs by increasing use of inadequately tested, costly products.
- The FDA's independent assessment of the benefits and risks of drugs and high-risk devices can help ensure that information is not communicated to physicians or patients that gives an incorrect impression of the utility of the product at issue (even if it isn't clearly "false")
- The Guthrie and Griffith discussion drafts suggest that disclaimers could help protect patients, but available evidence indicates that disclaimers on health-related promotional statements fail to adequately inform or modify consumer behavior
- Expanding off-label promotion would reduce manufacturers' incentives to conduct well-controlled trials of potential off-label uses in the first place, incentivizing manufacturers to seek approval of drugs and devices for the narrowest indication possible and then conduct "studies" of variable quality showing the utility of these products for unapproved indications that would not meet the current FDA standards for scientific rigor.

Chairman Burgess, Vice-Chairman Guthrie, Ranking Member Green, and other members of the committee:

My name is Aaron Kesselheim. I am an internal medicine physician, lawyer, and health policy researcher in the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women's Hospital in Boston and an Associate Professor of Medicine at Harvard Medical School. I lead the Program On Regulation, Therapeutics, And Law (PORTAL), an interdisciplinary research core that studies the intersections between laws and regulations and the development, utilization, and affordability of drugs. We are the largest, academic-based independent group conducting empirical research in this area in the country. Thank you for this opportunity to provide my views on the communication and marketing of medical products for off-label uses and the discussion draft documents from Reps. Griffith and Guthrie.

The current restrictions on manufacturers' ability to market their drugs for non-FDA-approved indications are not a bureaucratic or paternalistic effort to restrict manufacturers from communicating to physicians about their products. Rather, these rules were developed over the last century in response to major public health problems caused by the lack of regulation of manufacturer promotional activities. The notion that the FDA must validate a drug's or device's efficacy and safety was a response to public health tragedies in which patients died after taking products with poisonous constituents (sulfanilamide elixir, 1938), gave birth to babies with devastating congenital anomalies (thalidomide, 1962), or used contraceptive devices that caused bacterial sepsis (Dalkon Shield, 1974), all of which occurred in the context of wide manufacturer promotion of the safety of these products.¹ Even more common was the promotion of drugs to

¹ Kesselheim AS and Mello MM. Prospects for regulation of off-label drug promotion in an era of expanding commercial speech protection. *Univ North Carolina Law Review* 2014;92:1539-1604.

treat conditions for which they totally lacked efficacy. From these episodes, we learned, as former Chief Justice William Rehnquist put it, that “there are sufficient dangers attending [the] widespread use [of pharmaceuticals] that they simply may not be promoted in the same manner as hair creams, deodorants, and toothpaste.”² Rather, it was in the public’s interest for an independent body of experts—the FDA—to validate that a medication or high-risk device actually worked before it could be sold and promoted for a particular use.

Despite these rules, the past two decades has revealed that off-label promotion is quite common in the drug and medical device industries. Nearly every major drug manufacturer has now been investigated by government prosecutors for its off-label promotional practices. All of these cases also involved important risks to public health related to the off-label uses. A partial list of products for which inappropriate off-label marketing has led to patient morbidity and mortality includes:

- Rofecoxib (Vioxx), an anti-inflammatory drug linked to anywhere from 30,000 to over 130,000 heart attacks and sudden cardiac deaths because of inappropriate promotion.³
- Paroxetine (Paxil), an antidepressant promoted off-label for use in children, leading to 2 million prescriptions in children and adolescents in the year 2002 alone,⁴ that was linked to self-injury and suicide.⁵
- Numerous antipsychotic medications were prescribed to control behavioral symptoms in elderly patients with dementia, uses that were not only generally

² Virginia State Bd. of Pharmacy v. Citizens Consumer Council, 425 U.S. 748 (1976).

³ <https://www.finance.senate.gov/imo/media/doc/111804dgtest.pdf>

⁴ <http://www.bmj.com/content/351/bmj.h4629>

⁵ <http://www.bmj.com/content/351/bmj.h4320>

ineffective but that also increases the risk of death by 60 to 70%. Its promotion led to about one in 7 elderly nursing home residents receiving these drugs.⁶

Settlements of government investigations of these off-label marketing episodes have led to over \$15 billion in civil and criminal fines.

In these cases, the manufacturers were not necessarily going around spreading falsehoods about their products to get physicians to prescribe them. (That did happen on occasion, of course.) Rather, manufacturers and their promotional salespeople might present anecdotal evidence of benefits from uncontrolled case series. Or they might show doctors the results of observational studies that actually had important design flaws not recognizable unless someone had advanced training in pharmacoepidemiology. Or they might describe the results of clinical trials strategically designed to show favorable outcomes. In one study of off-label marketing practices that I led, we found that 75% of the cases involved self-serving presentations of the literature through which physicians were given unbalanced study data supporting the unapproved use.⁷ A common example was selective presentation of favorable studies, where dangers from the off-label uses allegedly being promoted were not mentioned. Other examples included presenting one drug as being superior to another when no head-to-head studies had been conducted and characterizing reports of individual cases or poorly designed studies as definitive evidence supporting an off-label use. In each of these particular cases, the words themselves may not have been false or strictly misleading, but physicians were given an incomplete picture of the use of the drug, leading to off-label prescribing and substantial patient harms. This is why we need the diligent, independent assessment of whether a drug or high-risk device is safe and effective for an intended use that is provided by the FDA, which

⁶ US Office of Inspector General. Medicare Atypical Antipsychotic Drug Claims for Elderly Nursing Home Residents. May 4 2011. Available from: <https://oig.hhs.gov/oei/reports/oei-07-08-00150.asp>

⁷ Kesselheim AS, Mello MM, Studdert DM. Strategies and practices in off-label marketing of pharmaceuticals: a retrospective analysis of whistleblower complaints. *PLoS Medicine* 2011;8(4):e1000431.

can involve dozens of scientists poring over extensive databases of studies in animals, toxicologic evaluations, and clinical trials.

However, the Griffith and Guthrie discussion drafts dangerously expand the permitted range of off-label statements for manufacturers. The Guthrie discussion draft defines “scientific information” that could support an off-label marketing claim as including “pre-clinical” data and all it requires is that a study was conducted that a manufacturer “anticipates could be sufficient” to support FDA approval and that the manufacturer “intend” that a supplemental application will be submitted at some undetermined time in the future. The Griffith draft, in creating a so-called “safe harbor” for scientific exchange, purports to require manufacturers to disclose the “appropriate contextual information” for their statements. But it would be highly risky to give a manufacturer with a strong financial and intellectual stake in the product’s success free rein to determine what is or isn’t proper context, or what is or isn’t contradictory, for its product. At the same time, it is unrealistic to expect each physician to have the time and expertise to subject such claims to the same kind of scrutiny that the FDA would exercise when it reviews a drug application or a request for a new indication. In these situations, we need the FDA to act as a learned intermediary on behalf of prescribing physicians, who can then synthesize the available data and make judgments about risks and benefits for their patients.⁸ The complexity of the assessment that is required, along with the high stakes of getting the assessment wrong, provides the rationale for having a formal drug-approval process in the first place.

The Griffith and Guthrie drafts also purport to protect the public health by attaching disclaimers to their vast expansions of manufacturers’ abilities to engage in off-label communication. I led a systematic review of the evidence about the impact of disclaimer related to health-related claims

⁸ Kesselheim AS and Avorn J. Pharmaceutical promotion to physicians and First Amendment rights. *New England Journal of Medicine* 2008;358:1727-1732.

of medical products.⁹ Most such data has been gathered in the context of promotional statements for herbal remedies and dietary supplements, for which Congress eliminated FDA oversight of promotion more than 20 years ago in the Dietary Supplement Health and Education Act of 1994. The result has been the proliferation of untested, ineffective, and frequently unsafe products that fill store shelves and patients' medicine cabinets and consume about \$32 billion of health care resources in the US, often with no demonstrable benefit. Many of these products advertise health-enhancing effects and bear disclaimers that the FDA has not evaluated the promotional claims, but the mass of collected evidence reveals that such disclaimers generally fail to adequately inform or modify consumer behavior. There is no scientific basis for believing that disclaimers would function any better in this context.

Expanding permitted off-label communications will expose patients to drugs that may not work or for which the safety has not been adequately established. It will also potentially divert use from drugs that we know have benefits that outweigh their risks because they have passed the usual FDA requirements. The result will also be increased health care costs, due to broader use of inadequately tested, costly products. Such effects are predictable because decades of evidence show that manufacturer promotion is a powerful force in shaping and directing physician prescribing and influencing physician knowledge in ways that favor the product being promoted, as opposed to the evidence-based practice. By contrast, the current system helps protect patients from widespread promotion of drugs and devices for potentially unsafe or ineffective off-label uses, while still permitting off-label prescribing at the discretion of physician and patients and providing well-

⁹ Kesselheim AS, Connolly JC, Rogers J, Avorn J. Despite mandatory disclaimers on dietary supplements, many consumers remain unaware or overlook the information. *Health Affairs* 2015;34(3):438-446.

circumscribed avenues for manufacturer communication about these uses, such as in response to bona fide questions arising from physicians.

Finally, the Griffith and Guthrie discussion drafts, if enacted into law, would reduce manufacturers' incentives to conduct well-controlled trials of potential off-label uses in the first place. Instead, manufacturers would be incentivized to seek approval of drugs and devices for the narrowest indication possible, and then conduct "studies" of variable quality showing the utility of these products for unapproved indications that would not meet the current FDA standards for scientific rigor.¹⁰ Many studies would predictably appear to support claims of efficacy, and those that best met marketing aims could be selected for emphasis in promotional campaigns, with the others relegated to footnotes or ignored. I strongly recommend that the committee not pursue these drafts and instead consider how we can give FDA the proper resources and authorities to continue to review emerging data efficiently so that evidence that does support new uses of drugs and devices can be incorporated into their labels and clinical practice, while uses that the totality of data show are unsafe can be identified for the benefit of patients.

¹⁰ Kesselheim AS, Mello MM, Avorn J. FDA regulation of off-label drug promotion under attack. *JAMA* 2013;309(5):445-446.