

January 9, 2017

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

**Re: Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products (Docket FDA-2016-N-1149)**

We write in response to the request for public comment, “Manufacturer communications regarding unapproved uses of approved or cleared medical products.” The FDA has requested input on “issues related to communications by manufacturers, packers, and distributors, including their representatives (collectively ‘firms’), regarding FDA-regulated drugs and medical devices for humans,” specifically unapproved uses of approved products.

These comments are submitted on behalf of:

- *The Fenway Institute at Fenway Health*, an interdisciplinary center for research, training, education and policy development focusing on national and international health issues;
- *Callen-Lorde Community Health Center*, which provides sensitive, quality health care and related services targeted to New York’s lesbian, gay, bisexual, and transgender (LGBT) communities — in all their diversity — regardless of ability to pay, while also promoting health education and wellness and advocating for LGBT health issues;
- *Treatment Action Group (TAG)*, an independent human immunodeficiency virus (HIV), hepatitis C virus (HCV), and tuberculosis research and policy think tank.

While allowing manufacturers to communicate freely with health care providers regarding off-label uses of their products could be beneficial to consumers in the short-term, there is a long-term need for a stronger evidence-base that would allow for FDA approval of these products. This issue is of particular concern for transgender patients utilizing hormones for gender affirmation, which are all currently administered off-label.

We understand that many drug, biologic, and device manufacturers are eager to communicate with healthcare providers regarding the off-label uses of their products. They argue that “truthful and non-misleading” scientific or medical information—beyond the safe harbors already allowed by the FDA, notably the exchange of scientific information—may help improve healthcare decision-making.<sup>1</sup> We acknowledge that a series of lawsuits, notably *United States v. Caronia*<sup>2</sup>, have ruled that this practice is within the First Amendment rights of manufacturers. We encourage the FDA to

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<sup>1</sup> Biotechnology Innovation Organization, Pharmaceutical Research and Manufacturers of America. Principles on responsible sharing of truthful and non-misleading information about medicines with health care professionals and payers. 2016 July. Available from: [https://www.bio.org/sites/default/files/PrinciplesReport\\_FINAL.pdf](https://www.bio.org/sites/default/files/PrinciplesReport_FINAL.pdf).

<sup>2</sup> 703 F.3d 149, 152 (2d Cir. 2012).

balance constitutional concerns regarding free expression with the agency's mandate, under the federal Food, Drug & Cosmetics Act (FDCA), to protect public health and safety.

The FDA's regulatory processes to ensure that drugs, biologics, and high-risk medical devices are safe and effective, both pre- and post-approval, are vital to the confidence and trust both healthcare providers and consumers have in the medical products used for various health indications. Expanding allowances for manufacturers to communicate with healthcare providers about their medical products in the absence of robust, independently verified data supporting safety and efficacy could undermine public health and endanger the American public.

Health care providers have been prescribing hormones for gender affirmation for decades. Scientific data on the efficacy and safety of hormones for gender affirmation exists.<sup>3</sup> However, on-label use should be based on a strong scientific evidence base, which should include dose comparison trials.

Because hormones have not been approved by the FDA for use in gender affirmation specifically, transgender people are forced to use hormones off-label for medically-necessary gender affirmation treatments. This can result in a multitude of health complications for many transgender people. We realize that the 1962 FDA Amendments prevent the FDA from making label recommendations without carefully performed studies that demonstrate "substantial evidence" of a drug's efficacy [i.e. the impact of a drug in a clinical trial setting].<sup>4</sup> Products necessary to the health of transgender patients need rigorous efficacy data from research with transgender people so that they may gain FDA-approval for gender affirmation.

We recognize that off-label use allowances have been essential to transgender women and transgender men, for whom hormone therapy to affirm gender identity is medically necessary.<sup>5</sup> We support such off-label use of hormones for gender affirmation. Neither estrogen for feminizing therapy nor testosterone for masculinizing therapy have received FDA indications, yet both are mainstay options for transgender women and transgender men undergoing medical gender affirmation.

In the absence of stringent FDA oversight of these products for gender dysphoria, prescribing practices are heavily dependent on evidence-based guidelines or statements issued by professional associations, including the American Medical Association and others. Additionally, review articles have been published in major peer-reviewed journals.

We recognize that healthcare providers caring for transgender women and men might benefit from manufacturers being able to communicate more freely about their products being used for feminizing and masculinizing purposes. For example, over the past 2 years there have been chronic shortages, including the ongoing shortage of 40 mg/mL formulations of injectable estrogen,

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<sup>3</sup> Murad MH, Elamin MB, Garcia MZ, et al. Hormonal therapy and sex reassignment: a systematic review and meta-analysis of quality of life and psychosocial outcomes. *Clin. Endocrinol. (Oxf.)* 2010;72(2):214–231.

<sup>4</sup> Junod SW, (2008). FDA and clinical drug trials: A short history. Davies M, Kerimani F, (eds.). *A Quick Guide to Clinical Trials*. Washington: Bioplan, Inc. 25-55.

<http://www.fda.gov/AboutFDA/WhatWeDo/History/Overviews/ucm304485.htm>

<sup>5</sup> Feldman J, Spencer K. Medical and surgical management of the transgender patient: What the primary care clinician needs to know. In: Makadon HJ, Mayer KH, Potter J, Goldhammer H, editors. *Fenway Guide to Lesbian, Gay, Bisexual, and Transgender Health 2nd Edition*. Philadelphia: American College of Physicians, 2015. P. 479-511.

which is frequently prescribed for transgender women requiring high-dose, low-volume administration of the hormone.<sup>6</sup> Clearer communication between manufacturers and providers about how this shortage is being resolved would be desirable.

However, we are concerned that expanding allowances for off-label communications by manufacturers could potentially harm transgender women and men. For example, manufacturers of hormonal products may want to communicate information intended to sway healthcare providers away from prescribing estrogen or testosterone for transgender individuals, or provide dosing and safety information that has not been fully validated. There may be a disincentive for manufacturers to encourage the prescription of off-label hormones for gender affirmation due to the potential for lawsuits or due to political pressure.

Ultimately, allowing manufacturers to engage in promoting off-label use of their products may not be in the best interests of transgender women, transgender men, and their healthcare providers. What is needed is for manufacturers to invest in the research and development necessary to meet existing new drug application (NDA) and supplemental NDA approval requirements, taking advantage of the expanded number of regulatory pathways currently in place to expedite and incentivize product registration.

There is still a dearth of high-quality data pertaining to the long-term safety of estrogen—often used at higher doses than those used by cisgender menopausal women—and limited comparisons with other estrogen modalities (e.g., patches and pills). Encouraging manufacturers to either conduct or support studies required to advance evidence-based treatment and care remains our priority. In the absence of these data, approvals by the FDA remain unlikely, healthcare providers and transgender individuals may not have access to information required to make informed treatment decisions, and public and private insurers may deny coverage for hormonal products not approved for their intended use.

We fear that liberalizing off-label marketing and promotion could not only result in an irreversible shift from the FDCA intended protections, but also lead companies to forego key research and development. By extension, this could negatively affect clinical care decision-making processes and scientific progress among key populations, including transgender women and transgender men.

We believe that any retreat from existing regulatory pathways required by manufacturers seeking to market drugs, biologics, or high-risk medical devices could result in equivocal evidence being used to support “truthful and non-misleading” promotion (or discouragement) of products for off-label use. We therefore urge the FDA to stand on principle and maintain its authority in ensuring the safety, efficacy, and evidence-based promotion of all prescription drugs, biologics, and high-risk medical devices.

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<sup>6</sup> Geffen S, Horn T, Smith KJ. Resolving the current injectable estrogen shortage: a public health imperative. Boston: Fenway Institute at Fenway Health; 2016. Available from: <http://fenwayhealth.org/wp-content/uploads/Resolving-the-current-injectable-estrogen-shortage-A-public-health-imperative.pdf>.