April 14, 2020

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

Re: Comments of NCLA in Support of Citizen Petition Filed on Behalf of the Coalition to Preserve Access to Pharmacogenomics (PGx) Information Docket No. FDA-2020-P-0152

Dear Sir or Madam:

The New Civil Liberties Alliance (NCLA) is pleased to submit these comments in support of the Citizen Petition filed on January 9, 2020 by Hyman, Phelps & McNamara, P.C. on behalf of the Coalition to Preserve Access to Pharmacogenomics (Pgx) Information (the Coalition). Pharmacogenomics, or PGx, generally refers to testing and research related to the impact of genetic variants on drug response. As the Citizen Petition explains, recent regulatory actions by the Food and Drug Administration (FDA) threaten to undermine the ability of clinical laboratories to provide healthcare professionals and patients with information critical to optimizing drug usage and avoiding adverse events. NCLA is filing these comments to focus on two concerns: (1) FDA's efforts to suppress truthful speech violate the First Amendment rights of clinical laboratories as well as those who wish to receive PGx information from those laboratories; and (2) FDA's defense of its speech suppression—it claims unlimited administrative discretion to prohibit the operation of *all* clinical laboratories but has chosen to exercise that discretion by prosecuting only those laboratories that disseminate truthful information of which FDA disapproves—cannot be squared with separation-of-powers principles of the U.S. Constitution.

Importantly, FDA does not assert that any of the contested PGx information is untruthful. Rather, it asserts that: (1) laboratory developed tests (LDTs) are medical devices subject to FDA regulation; (2) the Food, Drug, and Cosmetic Act (FDCA) prohibits the marketing of LDTs or other medical devices without advance approval or clearance from FDA; (3) although virtually none of the thousands of LDTs in use in this country have (or could obtain) the requisite approval, FDA will exercise enforcement discretion to permit most clinical laboratories that offer LDTs to continue to violate the law; (4) FDA's nonenforcement policy extends to clinical laboratories whose LDTs entail genetic testing, *provided that the laboratories do not convey information of a type to which FDA objects;* but (5) if those laboratories convey disfavored information, FDA will exercise its discretion to

bring enforcement actions against them. There is only one plausible label for FDA's conduct: speech suppression. FDA is taking enforcement action based solely on what laboratories say.

Such speech suppression is blatantly inconsistent with the First Amendment. FDA is attempting to regulate speech based on its content. The First Amendment's Free Speech Clause, subject only to narrow and well-understood exceptions that are inapplicable here, does not countenance governmental control over the content of messages conveyed by private individuals. *See, e.g. Texas v. Johnson* 491 U.S. 397, 414 (1989).

FDA cannot plausibly assert that PGx information provided by laboratories to doctors and patients is "commercial speech," a category of speech entitled to a somewhat reduced level of constitutional protection. Speech is "commercial" in character if it "proposes a commercial transaction." *Virginia State Bd. of Pharmacy v. Virginia Citizens Consumer Council, Inc.*, 452 U.S. 748, 762 (1976). Laboratories provide PGx information *after* they have entered into a commercial relationship with their clients and after they have conducted their PGx tests. The information they convey is no more "commercial speech" than are news stories distributed by the *Washington Post* to its paying customers.

Even if the laboratories are deemed to have engaged in commercial speech, FDA's speech suppression cannot pass constitutional muster under the somewhat-more-lenient commercial-speech standard. Under that standard, nonmisleading speech may not be restricted unless the government shows that its restriction directly and materially advances a significant government interest and is no more extensive than necessary to accomplish that purpose. *Central Hudson Gas & Electric Corp. v. Public Service Comm'n*, 447 U.S. 557 (1980). FDA asserts that permitting laboratories to convey PGx information raises safety concerns, yet it has provided no evidence to support that assertion. On the contrary, all available evidence suggests that prohibiting laboratories from conveying the disputed information will adversely affect patient outcomes. Nor has FDA explained why its safety concerns could not be ameliorated in a more narrowly tailored manner—such as by requiring laboratories to attach safety warnings to their statements.

FDA's assertion of unlimited discretion to bring (or not to bring) enforcement action against laboratories that market LDTs also raises serious separation-powers concerns. Article I of the U.S. Constitution vests *all* of the federal government's legislative power in Congress; in other words, only the people's elected representatives may adopt federal laws restricting individual liberty. As FDA interprets the FDCA, Congress has delegated to the agency sole authority to determine when the marketing of LDTs should be barred. The Constitution prohibits Congress from delegating its legislative powers in that manner. While

federal courts generally are not permitted to second-guess an agency's discretionary decision *not* to initiate enforcement action in a given instance, that doctrine is inapplicable here, where FDA has determined that it will, in fact, take action against specified laboratories that market LDTs.

FDA's position also raises significant due-process concerns because it deprives the regulated community of fair notice—and thus the ability to conform its conduct to FDA's expectations—and permits enforcement officials to make up the rules on the fly.

NCLA is also concerned that FDA's decision to prevent dissemination of PGx information will adversely affect public health. As FDA concedes, PGx can play an important role in identifying responders and non-responders to medications, avoiding adverse events, and optimizing drug dose. While *some* health-care-professionals have easy access to the research tools necessary to make appropriate prescribing decisions based on the results of genetic tests, many do not. If (as FDA insists) laboratories are barred from providing health-care professionals with the latest research regarding which drugs are most appropriate for patients with specific genetic makeups, patients are much more likely to be prescribed inappropriate drugs or dosages.

The recent COVID-19 pandemic provides a stark illustration of the dangers of unwarranted FDA interference in the work of laboratories that seek to develop and market LDTs. Laboratories have long been at the forefront of efforts to quickly develop tests for detecting the presence of new pathogens; they need considerable flexibility to meet the public's time-sensitive need for such tests. FDA's excessive regulation in this area has been blamed by many for delays in developing tests for the SARS-CoV-2 virus. In particular, FDA red tape delayed dissemination of an effective test developed by Dr. Alex Greninger, an epidemiologist at the University of Washington. FDA is repeating that mistake by continuing to interfere with truthful speech by laboratories whose LDTs entail PGx testing.

I. Interests of NCLA

The New Civil Liberties Alliance is a nonprofit, non-partisan civil rights group devoted to defending civil liberties. The "civil liberties" of the organization's name include rights at least as old as the U.S. Constitution itself, such as freedom of speech, due process of law, the right to be tried by an impartial and independent judge, and the right to live under laws made by the nation's elected lawmakers through constitutionally prescribed channels (*i.e.*, the right to self-government).

NCLA aims to defend civil liberties—primarily by asserting constitutional constraints on the administrative state. Although Americans still enjoy the shell of the Republic, a very different sort of government has developed within it—a type, in fact, that our Constitution was designed to prevent. This unconstitutional administrative state within the Constitution's United States is the focus of NCLA's concern.

FDA, as an agency of the Executive Branch, is authorized to execute laws adopted by the Legislative Branch. It lacks constitutional authority to legislate and then proceed to apply that legislation to the regulated community. Nor may FDA apply that legislation in a manner that violates constitutional norms, including freedom of speech and the right not to be deprived of life, liberty, or property without due process of law. NCLA is filing these comments because it agrees with the Citizen Petition that FDA's enforcement action violates each of those constitutional norms.

II. FDA's Statutory Authority

The Medical Devices Amendments (MDA) to the FDCA, adopted by Congress in 1976, authorized FDA for the first time to regulate medical devices. In general, the FDCA prohibits the manufacture or distribution of a complex medical device unless FDA has approved the manufacturer's application for premarket approval (PMA), 21 U.S.C. § 360e(a), or the manufacturer has properly notified FDA of its marketing plans under 21 U.S.C. § 360(k). The FDCA defines a medical device as "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is ... intended for use in the diagnosis of disease or other conditions, ... and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes." 21 U.S.C. § 321(h).

As FDA is well aware, its relatively recent determination that LDTs fall within the FDCA's "device" definition is highly controversial. For many years following adoption of the MDA, FDA did not assert regulatory authority over LDTs. It was generally understood that LDTs—which are not sold directly to consumers as "test kits" but rather are performed (at the request of licensed health-care practitioners) within the laboratories that developed the LDTs—are not medical devices because an LDT is not an "instrument, apparatus," etc. of the sort enumerated in the MDA. Instead, it was generally understood that the federal government regulated laboratories exclusively by means of the Clinical Laboratories Improvement Amendments of 1988, Pub. L. 100-578, 42 U.S.C. § 263a, a statute administered by the Centers for Medicare and Medicaid Services (CMS), not FDA.

FDA first attempted to regulate LDTs as medical devices in 2006. *See* FDA, Center for Device and Radiological Health, Office of In Vitro Diagnostic Device Evaluation and Safety, *Draft Guidance for Industry, Clinical Laboratories, and FDA Staff: In Vitro Diagnostic Multivariate Index Assays* (Sept. 7, 2006). FDA recognized, of course, the insurmountable obstacles that laboratories would face if required to obtain FDA approval/clearance for their LDTs as medical devices, and it also recognized the important public-health role of LDTs. So it announced that even though the FDCA prohibited laboratories from marketing LDTs without FDA medical-device approval, it would exercise its enforcement discretion not to bring enforcement actions against most such laboratories. Widespread marketing of LDTs without FDA approval continues.

In September 2006, Richard Samp (the principal author of these comments) filed a Citizen Petition that challenged FDA's legislative authority to regulate LDTs, particularly in the absence of notice-and-comment rulemaking. *See* Citizen Petition FDA-2006-P-0149. While NCLA strongly doubts FDA's legislative authority, these comments do not focus on that issue. We nonetheless note that the federal courts have not resolved the issue, which forms an important backdrop for the more specific issues raised by the Coalition's Petition.

III. Recent FDA Enforcement Activity

The Coalition is a group of diverse stakeholders (including laboratories) committed to giving health-care providers access to accurate information about the impact of genetic variances on drug response. As described more fully in the Petition, it is accepted throughout the scientific community (including by FDA) that people react differently to FDA-approved drugs based on differences in their genetic make-up. Some specific gene-drug associations are so well accepted that 385 drugs include PGx information in their FDA-approved labeling. For that reason, doctors routinely ask laboratories to undertake genetic testing of their patients, to assist the doctors in prescribing appropriate drugs/dosages for their patients. When they report the results of their testing, the laboratories routinely include truthful information relevant to individuals who possess the identified genes. For example, if a laboratory's test determines that the patient is a carrier of HLA-B*15:02, the laboratory is likely to include in its report the widely accepted finding that such individuals have a high risk of developing a potentially fatal reaction to the drugs carbamezapine and phenytoin.

In October 2018, FDA issued a Safety Communication warning to health-care providers and consumers about alleged dangers associated with PGx tests. FDA, *The FDA Warns Against the Use of Many Genetic Tests with Unapproved Claims to Predict Patient Response to Specific Medications: FDA Safety Communication* (Oct. 31, 2018). The Safety Communication focused on statements made by laboratories regarding the relationship

between genetic variations and the likely effects of specified medications, noting that laboratories had not obtained FDA approval to make statements of that nature. FDA simultaneously told laboratories that they should cease including information about specific medications in their laboratory reports for PGx tests unless and until FDA approved PMAs for the tests in question. FDA said that its directive applied even when the FDA-approved labeling for the medications in question includes information about PGx interactions.

One laboratory, Inova Genomics Laboratory (IGL), declined to commit that it would comply with FDA's prohibition against the dissemination of truthful PGx information. FDA responded by issuing a formal Warning Letter to IGL on April 4, 2019. The Warning Letter declared that IGL was operating in violation of the FDCA and gave IGL 15 days to notify FDA "of the specific steps your firm has taken to correct the noted violations, as well as an explanation of how your firm plans to prevent these violations, or similar violations, from occurring again." As FDA well knows, regulated entities cannot afford to ignore Warning Letters, which carry with them the implicit threat that FDA will seize company assets without further warning or legal process.

The Warning Letter denied IGL's assertion that there exists an LDT "exemption" for LDTs:

> FDA has not created a legal "carve-out" for LDTs such that they are not required to comply with the requirements under the [FDCA] that otherwise would apply. FDA has never established such an exemption. As a matter of practice, FDA, however, has exercised enforcement discretion for LDTs, which means that FDA has generally not enforced the premarket review and other FDA legal requirements that do apply to LDTs. Although FDA has generally exercised enforcement discretion for LDTs, the Agency always retains discretion to take action when appropriate such as when it is appropriate to address significant public health concerns.

Warning Letter at 2. The letter made clear that IGL is free to continue offering LDTs that provide genetic information; FDA objected solely to IGL's provision of PGx information in conjunction with its test results.

After the Coalition filed its Citizen Petition, FDA released a letter in February 2020 that may or may not represent a slight retreat from the speech-suppression policy announced in the Safety Communication and the Warning Letter. The letter has merely increased confusion among laboratories over how to comply with FDA requirements. Some laboratories (including IGL) have thrown in the towel and ceased providing any PGx

information in their reports. Other laboratories continue to provide such information but on a more limited basis.

IV. FDA's Speech Suppression Violates the First Amendment

FDA contends that LDTs are medical devices and that laboratories violate the FDCA by marketing LDTs lacking an FDA-approved PMA. In other words, the hundreds if not thousands of laboratories that market LDTs are criminals because few if any LDTs have FDA-approved PMAs. FDA chooses to overlook most of those alleged violations. But it has warned that it will bring enforcement action against one small group of LDT marketers: laboratories whose LDTs entail genetic testing and which include drug-specific information relevant to individuals possessing the identified genes. FDA's policy cannot be squared with the First Amendment.

FDA Regulates Speech, Not Conduct. FDA apparently argues that its policy regulates commercial conduct only (the marketing of unapproved medical devices), not speech. That argument does not pass the red-face test. FDA applies only one factor in determining whether to initiate enforcement action against laboratories that market LDTs: does the laboratory disseminate PGx information along with its test results? If yes, FDA initiates enforcement action. Under those circumstances, FDA's conduct can only be described as content-based speech regulation.

In analogous circumstances, the Supreme Court has rejected federal government efforts to characterize its enforcement policy as one focused on conduct and thus immune from First Amendment scrutiny. In *Holder v. Humanitarian Law Project*, 561 U.S. 1 (2010), the government argued that a federal statute prohibiting provision of "material support" to foreign terrorist organizations did not implicate the First Amendment because it regulated only conduct, not speech. The Court unanimously rejected that argument. Noting that the respondent wanted to convey his specialized knowledge of international law and effective petitioning techniques to a terrorist group, the Court concluded that any government effort to prevent him from conveying that particular message amounted to content-based speech regulation—to which strict First Amendment scrutiny applied. 561 U.S. at 27-28.[1]

[1] The Court also rejected the government's argument that speech coordinated with a foreign terrorist organization is analogous to "speech effecting a crime, like the words that constitute a conspiracy" and thus unprotected by the First Amendment. 561 U.S. at 27 n.3.

The Second Circuit has rejected a similar government argument in the context of speech by pharmaceutical manufacturers. Relying on First Amendment principles, the appeals court overturned the criminal conviction of a pharmaceutical salesman for conspiracy to distribute a misbranded drug, in violation of the FDCA. *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012). FDA had approved the drug in question (Xyrem) for some uses, but the defendant was accused of encouraging doctors to prescribe Xyrem for other uses not approved by FDA—by providing truthful information about Xyrem's effectiveness for those other uses.[2] The government argued on appeal that the First Amendment was inapplicable because Mr. Caronia was charged based on his actions (entering into a conspiracy to sell a misbranded drug), not his words. The Second Circuit rejected that argument, noting that prosecutors relied at trial almost exclusively on the words spoken by Mr. Caronia. 703 F.3d at 160-61. Similarly, when (as here) FDA decides to initiate enforcement action solely because it disapproves of statements made by laboratories that market LDTs, its actions implicate the First Amendment.

Nor may FDA avoid First Amendment scrutiny by arguing (as it has done occasionally in the past) that it is not restricting speech but rather is simply using speech as *evidence* that a regulated entity has acted with an improper intent. Government reliance on speech for evidentiary purposes does not implicate the First Amendment. Prosecutors may, for example, introduce evidence that a criminal defendant uttered racial epithets in order to prove that the defendant acted with the requisite racially discriminatory intent. *Wisconsin v. Mitchell*, 508 U.S. 476, 490 (1993). But that doctrine is inapplicable here. FDA is not focusing on statements by laboratories to prove that they are marketing LDTs without first seeking a PMA from FDA; indeed, there is no need for such proof because no laboratories have approved PMAs for their LDTs. Rather, FDA is relying on the laboratories' speech for one reason only: it disapproves of the content of that speech.

Strict Scrutiny Applies. FDA's speech restrictions are content-based; that is, FDA is threatening enforcement action because it objects to the content of the information being conveyed by some laboratories. Content-based speech restrictions are presumptively unconstitutional and subject to "strict scrutiny" review, under which the government must show that the regulation at issue is narrowly tailored to serve or promote a *compelling* government interest. *Nat'l Institute of Family and Life Advocates v. Becerra* ["*NIFLA*"], 138 S. Ct. 2361, 2371 (2018); *Brown v. Entertainment Merchants Ass'n*, 564 U.S. 786, 799

[2] Prosecutors alleged that the Xyrem became "misbranded" once it was offered for sale for a use not included within the FDA-approved labeling.

(2011). FDA has not attempted to articulate a "compelling" interest for its policy, and there is none.

Many of the targeted laboratories are fee-for-services enterprises. But the Supreme Court has never indicated that content-based speech restrictions are less objectionable when they target speech by commercial entities. On the contrary, *Sorrell v. IMS Health, Inc.*, 564 U.S. 552 (2011), rejected claims that a Vermont law imposing content-based speech restrictions should be subject to less-exacting constitutional scrutiny simply because the speech arose in a commercial context.[3] *NIFLA* catalogued the very limited instances in which strict scrutiny is inapplicable to laws that impose content-based speech restrictions (*e.g.,* state tort laws that "incidentally" burden the speech of professionals) without ever suggesting that "commercial speech" is one of them.[4]

FDA's speech restrictions are also speaker-based; they apply to only a small subset of laboratories and no one else. NCLA attorneys, for example, though lacking any medical training, are free to disseminate PGx information. Content-based speech restrictions are particularly suspect when they are imposed on some speakers and not others. *Sorrell* held that "strict scrutiny applies to regulations reflecting 'aversion' to what 'disfavored speakers' have to say." 564 U.S. at 564 (quoting *Turner Broadcasting System, Inc. v. FCC*, 512 U.S. 622, 658 (1994)).

FDA's speech restrictions are subject to strict scrutiny for an additional reason: the information being conveyed by laboratories to health-care professionals and patients is fully protected noncommercial speech. FDA's assertion that its speech restriction is subject to intermediate review under *Central Hudson* is based on the premise that laboratory reports are properly categorized as "commercial speech." That premise is faulty.

In general, "commercial speech" is defined as "speech which does no more than propose a commercial transaction." *Virginia State Bd. of Pharmacy*, 425 U.S. at 62. When

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[3] *Sorrell* held that "[s]peech in aid of pharmaceutical marketing ... is a form of expression protected by the First Amendment." *Id.* at 2659. The Court held that the Vermont law was subject to heightened scrutiny.

[4] *NIFLA* explained that "the Court has been especially reluctant to exempt a category of speech from the normal prohibition on content-based restrictions" and that "this Court's precedents do not permit governments to impose content-based restrictions on speech without persuasive evidence of a long (if heretofore unrecognized) tradition to that effect." *Id.* at 2372 (citations omitted).

a laboratory, after performing its LDT, writes a report about the test results, it is not proposing any sort of commercial transaction. Rather, by that point the customer has already engaged the laboratory's services, and the report does not solicit any additional business. The speech that FDA is regulating here is the actual product/service that laboratories are selling, not an offer to sell a separate product/service. Nor may FDA claim its policy merely regulates commercial speech by pointing to statements made by laboratories when advertising for customers; its policy is not limited to such statements but also seeks to suppress speech made after the test has been conducted.

The Supreme Court has explained that fully protected speech is not transformed into commercial speech merely because the speaker is drawing a salary (or otherwise seeking to maximize profits) while speaking. *Board of Trustees v. Fox*, 492 U.S. 469, 482 ("Some of our most valued forms of fully protected speech are uttered for a profit. See, e.g., *New York Times v. Sullivan*, 376 U.S. 254 (1964); *Buckley v. Valeo*, 424 U.S. 1 (1976) (per curiam)."). In *New York Times*, the Court granted full First Amendment protection to a newspaper for a paid advertisement in which the advertiser solicited monetary contributions.

FDA's policy restricts fully protected, noncommercial speech and does so in a content-based and speaker-based manner. In the absence of a "compelling" reason for FDA's speech restrictions, they cannot survive First Amendment scrutiny.

FDA's Speech Restrictions Cannot Survive Intermediate Scrutiny. Even if scrutinized under the intermediate standard of review normally applied to commercial-speech regulation, FDA's restrictions on laboratories' speech violate the First Amendment.[5] FDA cannot demonstrate that the restrictions directly advance a substantial government interest, nor do the restrictions qualify as a narrowly tailored means of achieving FDA's asserted interests.

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[5] In *Central Hudson*, the Supreme Court established a four-part test for determining whether a restriction on commercial speech complies with the First Amendment. Under *Central Hudson*, the government may regulate commercial speech that (1) is not inherently misleading and concerns "lawful activity," only upon a showing that: (2) the government has a substantial interest that it seeks to achieve; (3) the regulation directly advances the asserted interest; and (4) the regulation serves that interest in a narrowly tailored manner. *Central Hudson*, 447 U.S. at 566. NCLA notes, however, that several recent decisions suggest that the Supreme Court is moving away from the more lenient *Central Hudson* standard and may apply the same First Amendment review standard to restrictions on commercial speech that it applies to restrictions on noncommercial speech. *See, e.g., NIFLA*, 138 S. Ct. 2361; *Reed v. Town of Gilbert*, 136 S. Ct. 2218 (2015).

The First Amendment does not bar FDA from prohibiting false or misleading commercial speech. But FDA is seeking to prohibit an entire category of speech without regard to its truthfulness. Nor does FDA seriously contest the truthfulness of much of the PGx information that laboratories convey to health-care professionals. The information is often taken directly from an FDA-approved label. Other information is supported by adequate evidence (*e.g.,* well-designed clinical studies) of PGx gene-drug associations.

FDA's October 2018 "Safety Communication" expressed concern that some laboratories were making unsubstantiated claims about PGx gene-drug associations. It stated, for example, "FDA is aware of genetic tests that claim results can be used by physicians to identify which antidepressant medications would have increased effectiveness or side effects compared to other antidepressant medications. However, the relationship between DNA variations and the effectiveness of antidepressant medications has never been established." Safety Communication at 2. FDA warned that changes to patients' medications based on such information "could potentially lead to patient harm." *Id.* If so, FDA may have a substantial interest in restricting claims regarding antidepressant medications. But concern about lack of substantiation for one narrow set of claimed PGx gene-drug associations cannot justify prohibiting all dissemination of PGx information. Any such across-the-board ban cannot pass muster under *Central Hudson*'s narrow tailoring requirement. Indeed, FDA admits that PGx testing can be beneficial to some patients. *Id.* at 1 ("The use of some drugs can be aided by pharmacogenetic testing; there is sufficient scientific evidence demonstrating a relationship between certain drugs and genetic variants."). FDA has no substantial interest in preventing laboratories from conveying PGx information to patients when adequate evidence of PGx gene-drug associations exists.

FDA employs many talented scientists. But given rapid advancements in the field, FDA officials cannot possibly keep up with all emerging evidence of PGx gene-drug associations. Simply because FDA officials have not yet reviewed the evidence does not undermine its validity. As one federal court explained, in an opinion striking down an FDA speech-suppression policy on First Amendment grounds:

> [I]n asserting that any and all scientific claims about the safety, effectiveness, contraindications, side effects, and the like regarding prescription drugs are presumptively untruthful or misleading until FDA has had the opportunity to evaluate them, FDA exaggerates its overall place in the universe.

Washington Legal Found. v. Friedman, 13 F. Supp. 2d 51 (D.D.C. 1998).

Under the third prong of the Central Hudson test, FDA bears the burden of demonstrating that its speech restrictions "directly advance the state interest involved; the regulation may not be sustained if it provides only ineffective or remote support for the government's purpose." *Central Hudson*, 447 U.S. at 564. In order to satisfy that requirement, "a government body seeking to sustain a restriction on commercial speech must demonstrate that the harms it recites are real and that its restrictions will in fact alleviate them to a material degree." *Edenfield v. Fane*, 507 U.S. 761, 770-71 (1993). "[M]ere speculation or conjecture" is insufficient to fulfill the requirements. *Id.* at 770. FDA cannot meet its burden merely by hypothesizing that the failure to ban all dissemination of PGx information by laboratories "could potentially lead to patient harm." To support its speech-suppression policy, FDA must demonstrate that patients will, in fact, be harmed if anything less drastic than a total speech ban is imposed. FDA has produced no such evidence to date.

FDA may be concerned that health-care professional might be misled into believing that every PGx gene-drug association reported by a laboratory has been confirmed by FDA. If so, the obvious, more-narrowly tailored response is to require the laboratory to state explicitly whether reported gene-drug associations have been recognized by FDA. Courts have repeatedly held that banning commercial speech altogether is impermissible when the government's substantial interest can be satisfied through a disclaimer requirement. *See, e.g., Pearson v. Shalala*, 164 F.3d 650, 657 (D.C. Cir. 1999).

In sum, FDA's speech suppression policy cannot survive First Amendment scrutiny even if evaluated under the somewhat more lenient standards applicable to commercial speech.

V. FDA's Policy Raises Serious Separation-of-Powers and Due-Process Concerns

FDA's speech suppression policy is unconstitutional for the additional reasons that: (1) separation-of-powers principles prohibit FDA from exercising legislative power in this manner; and (2) Executive Branch officials exercising virtually unlimited discretion regarding how to enforce the law violates the Due Process Clause.

As FDA interprets the FDCA, Congress—in violation of Article I of the Constitution—has delegated to FDA unbridled authority to exercise legislative authority over laboratories that offer LDTs. The Supreme Court has held repeatedly that Article I's grant of "[a]ll legislative Powers" to Congress means that Congress may not transfer to others "powers which are strictly and exclusively legislative." *Wayman v. Southard*, 23 U.S. (10 Wheat.) 1, 42-43 (1825). Writing for the Court, Chief Justice John Marshall explained that while Congress may delegate to another branch of government the task of "fill[ing] up the

details" of legislation, Congress itself must perform the task of announcing overriding general policies. *Id*. at 31, 43.[6]

As Justice Gorsuch has explained:

> If Congress could pass off its legislative power to the executive branch, the "[v]esting [c]lauses, and indeed the entire structure of the Constitution," would "make no sense." Without the involvement of representatives from across the country or the demands of bicameralism and presentment, legislation would risk becoming nothing more than the will of the current President.

Gundy v. United States, 139 S. Ct. 2116, 2134-35 (2019) (Gorsuch, J., dissenting) (quoting Gary Lawson, *Delegation and the Original Meaning*, 88 Va. L. Rev. 327, 340 (2002)).

According to FDA, the FDCA prohibits laboratories from offering LDTs, except in accordance with rules developed by FDA at its sole and unbounded discretion. Under FDA's view, Congress did not simply delegate to FDA the task of "filling up the details"; it delegated the task of creating the overriding general policies governing whether and when laboratories are permitted to market LDTs in the absence of a PMA. When Congress has delegated to others authority to adopt binding laws without articulating any policies to guide the exercise of that authority—nor even establishing an intelligible principle underlying its delegation—the Court has struck down the delegation as a violation of Article I, § 1 of the Constitution. *See, e.g., Panama Refining Co. v. Ryan*, 293 U.S. 388, 430 (1935). Either the FDCA represents an unconstitutional delegation of legislative authority or FDA has misinterpreted the FDCA. Under either scenario, FDA's current policy—which applies a speech-suppression policy to a small group of laboratories that market LDTs—cannot stand.

As interpreted by FDA, the FDCA also violates the Due Process Clause's void-for-vagueness doctrine. The Supreme Court has explained that doctrine as follows:

> The Fifth Amendment provides that "[n]o person shall ... be deprived of life, liberty, or property, without due process of law." Our cases establish that the

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[6] John Locke—whose views on separation of powers were highly influential among the Founding Generation—wrote, "The legislative cannot transfer the power of making laws to any other hands; for it being but a delegated power from the people, they who have it cannot pass it over to others." John Locke, The Second Treatise of Civil Government and Letter Concerning Toleration § 141, p. 71 (1947).

> Government violates this guarantee by taking away someone's life, liberty, or property under a criminal law so vague that it fails to give ordinary people fair notice of the conduct it punishes, or so standardless that it invites arbitrary enforcement. *Kolender v. Lawson*, 461 U.S. 352, 357–358 (1983). The prohibition of vagueness in criminal statutes "is a well-recognized requirement, consonant alike with ordinary notions of fair play and the settled rules of law," and a statute that flouts it "violates the first essential of due process." *Connally v. General Constr. Co.*, 269 U.S. 385, 391 (1926).

Johnson v. United States, 135 S. Ct. 2551, 2556-57 (2015).

FDA's interpretation of the FDCA (a criminal statute) raises both of the void-for-vagueness concerns identified by *Johnson*. It fails to provide ordinary people fair notice of the conduct it punishes; indeed, even following FDA's February 2020 letter, laboratories are still in the dark regarding precisely what PGx information (if any) FDA will permit them to convey in conjunction with their LDT reports. More importantly, the FDCA (as interpreted by FDA) is "so standardless that it invites arbitrary enforcement." *Id.* at 2556. FDA claims the authority to pick and choose which laboratories it will prosecute (in conjunction with the Department of Justice), based on its own policy preferences. Such boundless prosecutorial authority is inconsistent with Due Process Clause constraints.

VI. FDA's Policy Will Adversely Affect Public Health

NCLA is concerned that FDA's decision to prevent dissemination of PGx information will adversely affect public health. Indeed, FDA's decision is difficult to reconcile with FDA's recognition that "[p]harmacogenomics can play an important role in identifying responders and non-responders to medications, avoiding adverse events, and optimizing drug use." FDA, *Table of Pharmacogenomic Biomarkers in Drug Labeling*, https://www.fda.gov/drugs/science-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling.

FDA states that pharmacogenomic considerations can be adequately accounted for by relying on the research skills and professional judgment of the prescribing physicians, without the need for laboratories to provide physicians with PGx information. For reasons explained at length in the Petition, placing sole reliance on the prescribing physician creates too great a risk that important PGx information will be missed—thereby endangering patient safety.

NCLA will not repeat that entire explanation here. We write separately to note that clinical laboratories have the resources to remain up-to-date on rapidly evolving PGx research, resources that individual physicians lack. Most physicians and other health-care professionals do not have the time and resources to review each genetic variant result and then compare it against all relevant individual drug labels, not to mention conducting research to find relevant PGx information from literature and clinical guidelines. Indeed, doctors have come to rely on laboratory reports as their principal source of updated information. According to the Association for Molecular Pathology, "As the prevalence of phamacogenetic testing continues to increase, so will the need for laboratory professionals to translate genetic laboratory results to healthcare providers who make prescribing decisions for patient care." Association for Molecular Pathology, *Position Statement: Best Practices for Clinical Pharmacogenomic Testing*, 1 (Sept. 4, 2019). FDA's policy blocks this source of vital safety-related information.

The delays recently experienced by laboratories in developing LDTs to detect the presence of the SARS-CoV-2 virus—unnecessary delays caused largely by excessive FDA red tape—ought to persuade FDA that its excessive regulation of LDTs poses serious public-health risks. Those delays prevented public-health officials from conducting tests for the virus during crucial weeks in February and March 2020.

We note initially that FDA's overly expansive definition of a medical device—a definition that tells laboratories that they violate the criminal law by marketing LDTs without an approved PMA (an approval that most laboratories cannot realistically obtain)—no doubt discourages many laboratories from offering LDTs. But despite that discouragement, many laboratories around the country began working on developing in-house diagnostic tests in January 2020 when the threat of a world-wide COVID-19 pandemic began to take shape. Those laboratories moved forward in reliance on FDA's stated policy of exercising its discretion not to bring enforcement actions against most marketers of LDTs.

But then on January 31, 2020, the U.S. Department of Health and Human Services declared a health emergency in the United States in response to the COVID-19 pandemic. That declaration was intended to give FDA flexibility to speed up approval for critical medical products. But under FDA rules, the declaration imposed a new limitation on laboratories: they were barred from marketing LDTs to test for the novel coronavirus without an "emergency use authorization" (EUA) from FDA.

The unnecessary delays experienced by laboratories in obtaining EUAs during February and March 2020 are described in detail in a recent Washington Post article. *See* Washington Post, *For Weeks, Scientists Alarm Over Flawed Test Grew*, A1 (April 4, 2020).

Particularly unsettling was the experience of Alex Greninger, an assistant director of the University of Washington clinical virology lab. He developed his own LDT for COVID-19 in early February—at a time when the only FDA-approved test kit (one developed by the Centers for Disease Control and Prevention in Atlanta) was proving to be defective. However, the approval process for his EUA was painfully slow.

Greninger spent more than 100 hours filing out the 38-page EUA form and collecting information needed for the application. He emailed the application to FDA on February 18, only to be told that the application could not be accepted because it had to be mailed to Washington, DC on a hard disk. Greninger complied, but FDA later determined that his EUA application contained insufficient data—in part because his LDT did not test for *other* diseases such as SARS and Ebola. On February 28, Greninger and other clinical scientists appealed to Congress that FDA was creating too many roadblocks to testing approval and said, "Notably, no test manufacturer or clinical laboratory has successfully navigated the EUA process for SARS-CoV-2 to date." Only then did FDA revise its EUA-approval process; it announced on February 29 that laboratories could begin testing patients as soon as they notified FDA and would not have to submit paperwork for 15 days. Greninger's laboratory began testing patients on March 2 and was soon testing thousands of patients each day with a high degree of accuracy. But FDA red tape delayed wide-spread testing by more than two weeks, a period during which the novel coronavirus spread rapidly and virtually no Americans were tested. It is widely acknowledged that earlier widespread testing might have helped considerably in containing the spread.

The lesson is clear: although FDA claims to have adopted its speech-suppression policy to protect the health of patients, FDA restrictions on the marketing of LDTs are far more likely to cause harm than to benefit public health. Testing and research related to the impact of genetic variants on drug response develops rapidly, sometimes in response to new drugs developed to treat emerging pathogens such as SARS-CoV-2.[7] Unless laboratories are free to respond to such challenges by disseminating truthful information about gene-drug associations for those new drugs, patients will be denied optimal treatment.

[7] NCLA notes that Dr. Jean-Laurent Casanova, a physician at Rockefeller University Hospital, "suspects that vulnerability to [SARS-CoV-2] among some young people may be partly encoded in their DNA." He is studying genetic samples from young, severely ill COVID-19 patients, with a goal of identifying gene-based vulnerabilities and ultimately developing "a cure." Washington Post, *Hundreds of Young Americans Have Been Killed by the Coronavirus, Data Shows*, A1 (April 9, 2020).

CONCLUSION

NCLA respectfully requests that FDA grant the Citizen Petition filed by the Coalition. The agency should rescind its speech-suppression policy for laboratories that engage in PGx testing. Any new FDA policy on PGx tests should by developed through a notice-and-comment rulemaking proceeding that complies with the Administrative Procedure Act. Even assuming that FDA possesses the statutory authority required to support promulgating a new rule, FDA should limit its future enforcement activity to laboratories shown to have disseminated information that is not accurate—be it related to PGx data, COVID-19 data, or some other LDT result.

Sincerely,

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