



American
Clinical Laboratory
Association

September 18, 2019

Ned Sharpless, M.D.
Acting Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Jeffrey Shuren, M.D., J.D.
Director, CDRH
U.S. Food and Drug Administration
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Timothy Stenzel, M.D., Ph.D.
Director, Office of Health Technology 7, CDRH
U.S. Food and Drug Administration
10903 New Hampshire Avenue
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Re: FDA Actions on Pharmacogenetic Testing

Dear Drs. Sharpless, Shuren, and Stenzel:

In the past several months, FDA has taken significant and troubling actions directed at pharmacogenetic (PGx) testing. Without engaging key stakeholders, FDA has demanded that laboratories stop offering PGx tests – including laboratory developed tests (LDTs) – that reference specific drugs or drug classes unless approved by FDA.

ACLA is deeply concerned about FDA's actions, which will have the practical effect of taking away actionable information relied upon by health care professionals every day to make informed prescribing decisions. This will negatively impact patient care and increase medical costs, especially in situations where there is not an FDA-cleared or approved alternative to a PGx test. Moreover, LDTs are not medical devices and in recent years ACLA has been engaged in ongoing discussions with FDA and Congress on enacting a new statutory framework for diagnostic regulation. Now, in the middle of those discussions, FDA has effectively banned a critical subset of LDTs. These actions not only undermine progress in developing a comprehensive legislative solution but also amount to an inappropriate form of backdoor regulation of LDTs.

ACLA requests that FDA reconsider its approach toward PGx testing. To facilitate a productive dialogue, we request a meeting with you, as well as representatives of the Center for Drug Evaluation and Research (CDER). We will be reaching out directly to Dr. Sharpless's office to schedule a meeting.

Background on PGx Testing and FDA's Actions

PGx tests identify genetic markers that provide actionable information to help assess a patient's likely response to drugs, based on well-documented scientific and clinical evidence. This information informs health care professionals as they determine whether the prescribing of a specific drug or drug class may be unsafe or ineffective (such as doses needing to be adjusted for optimal value or whether identified side effects are more likely to occur), thus providing a significant improvement in patient care. Additionally, according to FDA's own figures, the cost of

drug-related morbidity and mortality exceeds \$136 billion annually.¹ By identifying those patients more likely to suffer adverse drug reactions as well as non-responders, PGx testing helps limit the enormous costs associated with “trial and error” approaches to prescribing.

Notwithstanding the benefits of PGx testing, FDA has taken a series of actions that will dramatically undermine the availability and future development of PGx testing. As described below, FDA’s actions are not based on any new statutory authority, regulation, or even a guidance document. Instead, the Agency’s new “policy” has been implemented through a safety notification, a warning letter, and informal, non-public communications to laboratories. First, on October 31, 2018, FDA issued a “safety notification” warning patients and physicians against the use of PGx tests that claim to predict response to specific medications.² Other than references to physicians making “inappropriate changes to a patient’s medication,” FDA cited no actual safety issues associated with PGx tests or other data supporting the Agency’s actions. FDA cited only one type of PGx testing as lacking scientific support – tests that claim to guide antidepressant therapy – but it issued a statement warning against *any* PGx test. FDA’s notification was issued without any advance engagement with key stakeholders.

Second, as stated in FDA’s safety notification, FDA then reached out to several firms offering PGx tests to demand that they revise their test reports and labeling, or withdraw such tests. Most firms addressed the FDA’s concerns by removing specific medication names from patient test reports and informational material. One laboratory, Inova Genomics Laboratory, declined to take these actions. FDA responded by issuing a Warning Letter.³

Third, in late July of this year, more clinical laboratories began to receive telephone calls and emails from FDA. In these communications, the Agency demanded that laboratories remove any claims referencing specific medications *or drug classes*, until FDA reviewed such claims through a premarket submission. These demands went well beyond the October 2018 safety notification, which only restricted references to specific medications. Moreover, it is not clear whether the restrictions are the same for all clinical laboratories contacted. Apparently some laboratories were permitted to report predicted phenotype, while others were told by FDA that they could report genotype results only.⁴ Other laboratories were told that they could not even reference drug labeling approved by FDA, which conflicts with FDA’s October 2018 safety notification and defies common sense.⁵

FDA’s Actions will Undermine the Public Health and Increase Costs

FDA’s actions on PGx tests will have a number of practical effects. Without necessary context about the relationship of genetic variants to specific drugs, prescribers and patients are left without clinically vital information. Patients whose genetic makeup indicates that a specific drug will be effective – or will cause an adverse reaction – will be directly and immediately harmed by

¹ FDA, *Preventable Adverse Drug Reactions: A Focus on Drug Interactions* (Mar. 6, 2018) (citing Johnson JA, Bootman JL. Drug-related morbidity and mortality. A cost-of-illness model. *Arch Intern Med* 1995; 155(18):1949–1956).

² 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).

³ FDA, Warning Letter to Inova Genomics Laboratory (Apr. 4, 2019).

⁴ Phenotype (e.g., CYP450 metabolic phenotype) is the basis for recommendations in the scientific literature, in widely-accepted consensus standards, and on FDA drug labels for most PGx test results.

⁵ Even if FDA permits laboratories to reference drug-gene associations that are reflected in FDA-approved drug labels, that is a wholly inadequate solution. Drug labels are inconsistently updated and often do not reflect the current state of science. There are many drugs for which strong evidence and widely-accepted guidelines exist reflecting a PGx association, but for which there is no mention of PGx in the drug label.

FDA's actions. Furthermore, FDA compounds the harm by requiring laboratories to withhold information even about drug classes, which can guide a physician towards or away from a broad group of drugs that will help or harm the patient. What FDA is doing will result in more patients getting a less effective or the wrong medication, with negative consequences for patient care and health care costs. Additionally, by implementing an effective ban, FDA will chill investment and innovation in the PGx space.

FDA's position conflicts with recommendations of scientific societies, such as the Association for Molecular Pathology (AMP). AMP has published recommendations on how laboratories that offer PGx testing should communicate information to prescribers. As stated by AMP "[p]harmacogenomic testing provides the greatest clinical benefit to patients when the healthcare provider is able to easily determine when an actionable prescribing change and/or treatment decision is indicated by a patient's genotype."⁶ Therefore, AMP recommends that "information regarding the test's interpretation," including a "list of the drugs for which responsiveness may be affected by the genotype," should be included in a PGx laboratory report.

Rather than banning PGx testing, FDA should encourage responsible LDT development by adopting recommendations such as those offered by AMP and formally recognizing existing peer-reviewed, evidence-based guidelines as a basis for establishing clinical validity of a PGx test. These include guidelines issued by the Clinical Pharmacogenetics Implementation Consortium (CPIC) and NIH-sponsored PharmGKB. For example, CPIC systematically assigns levels to evidence to drug-gene associations and publishes guidelines on the strength of each prescribing recommendation.⁷ PharmGKB curates available literature about clinically actionable gene-drug associations and genotype-phenotype relationships.⁸ At the very least, FDA should permit laboratories to use these guidelines and recommendations as the bases for selecting which genetic variants to include in clinical reports and how to appropriately convey information to prescribers.

FDA's Actions Undermine Congress and Ongoing Legislative Efforts

In recent years, FDA has acknowledged that new legislative authority should be enacted before FDA regulation of LDTs.⁹ ACLA agrees that the time has arrived to design an appropriate new, comprehensive statutory framework specifically designed for diagnostics. In recent years, ACLA has engaged with FDA and Congress to offer its insights and expertise on clinical laboratories to better inform the creation of such a framework. Members of Congress have circulated legislative discussion drafts that would enact a comprehensive regulatory system for diagnostics.

However, FDA's recent actions related to PGx tests undermine the very legislative efforts that FDA says it supports. For example, one of the key features of the legislative discussion drafts is a grandfather provision for existing LDTs. By effectively taking PGx LDTs off the market prior to enacting a new statutory framework, FDA is gutting the effectiveness of the grandfather provision. In addition, FDA's actions reinforce longstanding concerns that affording FDA unchecked

⁶ See Association for Molecular Pathology Position Statement: Best Practices for Clinical Pharmacogenomic Testing, available at [https://www.amp.org/AMP/assets/File/position-statements/2019/Best Practices for PGx 9 4 2019.pdf?pass=96](https://www.amp.org/AMP/assets/File/position-statements/2019/Best_Practices_for_PGx_9_4_2019.pdf?pass=96)

⁷ See What is CPIC, available at <https://cpicpgx.org/>

⁸ See What is PharmGKB, available at <https://www.pharmgkb.org/whatIsPharmgkb/prescribing>

⁹ See Speeches by FDA Officials, Scott Gottlieb, M.D., *Remarks at the American Clinical Laboratory Association Annual Meeting* (Mar. 6, 2018) (stating that "comprehensive legislation is the right way to address" LDTs); Turna Ray, *Lab Industry Queries FDA About Concerns Over VALID Act*, 360DX (Mar. 27, 2019) (describing then-FDA Chief of Staff Lauren Silvis reiterating the same position).

discretion could result in FDA overextending its authority based solely on a claimed concern for public health, without any scientifically valid, documented basis for the alleged concern.

In short, ACLA believes that FDA should be focused on moving comprehensive diagnostic legislation forward, not taking unilateral actions that undermine that effort.

FDA's Actions Raise Significant Legal Issues

As ACLA has detailed in other settings, FDA lacks authority under current law to regulate LDTs as medical devices.¹⁰ But even putting aside FDA's lack of jurisdiction, the Agency's actions raise several other legal concerns. First, in imposing an overly-broad and inconsistently-applied policy, FDA's actions are contrary to the Administrative Procedure Act (APA), in that they are "arbitrary, capricious, an abuse of discretion, [and] otherwise not in accordance with law."¹¹ Nor has FDA followed the APA's notice and comment rulemaking requirements despite imposing new and effectively binding policies. Second, FDA's actions interfere with the authority of health care professionals to prescribe, order, or use PGx test results. This is a clear encroachment on the practice of medicine, which the Agency does not have authority to regulate. Third, in barring laboratories from communicating truthful, non-misleading scientific data and information to health care professionals, FDA's actions raise serious First Amendment issues.

Conclusion

FDA's actions have the practical effect of taking away valuable tools that physicians rely on for making informed prescribing decisions. Given that physicians will be forced to revert to older methodologies (such as try and fail, try and maybe succeed) in order to make prescribing decisions without actionable genomic information, it is likely that FDA's new policy will result in more patients receiving less than optimal medications or doses, with consequent safety and cost ramifications. Moreover, the Agency's actions threaten to bring the pace of innovation and investment in PGx testing to a halt.

For all of these reasons, ACLA requests a meeting to engage with FDA leadership on this topic. We look forward to a productive dialogue with FDA in the near future. In the meantime, should you have any questions about this letter, please feel free to reach me at 202-637-9466 or jkhani@acla.com.

Sincerely,



Julie Khani
President, ACLA

¹⁰ See, e.g., Paul D. Clement & Laurence H. Tribe, *Laboratory Testing Services, As The Practice of Medicine, Cannot Be Regulated As Medical Devices* (Jan. 6, 2015).

¹¹ 5 U.S.C. § 706(2)(A).