

February 2, 2015

Margaret A. Hamburg, MD
Commissioner
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Proposed “Framework for Regulatory Oversight of Laboratory Developed Tests” and proposed
“Notification and Medical Device Reporting for Laboratory Developed Tests”

Dear Commissioner Hamburg:

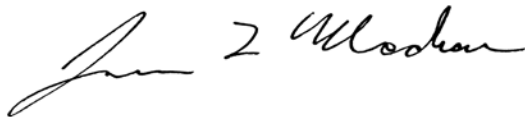
On behalf of the physician and medical student members of the American Medical Association (AMA), I appreciate the opportunity to provide comments on the U.S. Food and Drug Administration’s (FDA) proposed “Framework for Regulatory Oversight of Laboratory Developed Tests” (proposed Framework) and proposed “Notification and Medical Device Reporting for Laboratory Developed Tests” (proposed Notification). While the AMA is offering extensive comments and recommendations, included as an enclosure, we strongly urge that the Agency provide the public and interested stakeholders with a comprehensive environmental assessment of laboratory medical practices and procedures that have prompted the issuance of this proposed new regulatory regime. It is overly broad and highly likely to disrupt clinical care. In short, the proposed guidance will compromise patient access to standard of care testing, stifle innovation, and could undermine important public health goals such as, newborn screenings and detection of bio-threats and infectious disease outbreaks.

The AMA is very encouraged by the commitment of this Administration, as outlined in the State of the Union Address, to further the medical strides realized by the Human Genome Project with a major initiative to map a million genomes and improve translation to medical care through funding and support to the National Institutes of Health. However, the AMA has serious concerns that our shared vision for rapidly advancing clinical knowledge and the application of it to patient care will be stymied by the FDA’s proposed Framework and proposed Notification. We urge the Agency to rescind the proposed guidance documents. Instead, we ask the FDA to engage with physicians who provide these services, clinical laboratories, and other stakeholders, including the Centers for Medicare & Medicaid Services (CMS) and the Centers for Disease Control and Prevention (CDC), to map out a modernization pathway that will further accelerate discovery and the widespread availability of precision medicine. This approach is essential to avoid the upheaval and disruption that will occur should the FDA finalize the proposed guidance. As drafted, it will negatively impact the ability of physicians to provide standard of care testing services and limit the use of any future publicly funded NIH research that is clinically validated by physicians to guide patient care.

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The AMA also firmly believes that the FDA lacks statutory authority to regulate physician services and procedures. To the extent such authority exists, the FDA must issue this guidance through notice and comment rulemaking. Despite our legal objections, the AMA appreciates the efforts of the FDA to propose a laboratory developed testing services Framework and Notification requirements that are risk-based, are phased-in, and include a number of enforcement discretion carve-outs for categories that the Agency has described as traditional, rare disease, and unmet need laboratory developed testing services. We strongly urge the Agency to consider the enclosed recommendations related to the process going forward and necessary modifications needed to the guidance documents including the carve-outs. At a minimum, we urge the FDA, CMS, and the CDC to jointly issue another draft of the proposed requirements before finalizing the guidance to avoid duplication and confusion. If you have any questions, please contact Margaret Garikes, Vice President of Federal Affairs, at 202-789-7409 or margaret.garikes@ama-assn.org.

Sincerely,

A handwritten signature in black ink, appearing to read "James L. Madara". The signature is written in a cursive style with a large initial "J" and "M".

James L. Madara, MD

Attachments

Executive Summary

Physicians who provide laboratory developed testing services are an essential member of a patient's medical team and the services and procedures they offer are vital to the practice of medicine impacting the majority of patients across the nation. A wholesale change in oversight of clinical laboratories and physicians who provide such services and procedures must not only be consistent with the law, but must adequately account for the clinical realities of health care delivery, innovations by physicians, protection of public health, and patient access to essential medical services.

Overarching Recommendations

In the interest of safeguarding patient access to existing standard-of-care testing services and the innovation that has inspired development and provision of new cutting-edge testing procedures, the AMA urges the Food and Drug Administration (FDA or Agency) to:

- **Withdraw the proposed “Framework for Regulatory Oversight of Laboratory Developed Tests” (proposed Framework) and the proposed “FDA Notification and Medical Device Reporting for Laboratory Developed Tests” (proposed Notification).** The Agency must rescind the proposed Framework and Notification as the Agency lacks statutory authority to regulate physicians engaged in the practice of medicine, which includes the procedures, services, and analyses that physicians perform in clinical laboratories.
- **Collaborate with the Centers for Medicare & Medicaid Services (CMS) to modernize the existing Clinical Laboratory Improvement Amendments (CLIA) regulations.** The FDA is able to provide technical assistance to CMS along with the Centers for Disease Control and Prevention (CDC) to, among other things, strengthen the role of third-party accreditors and the infrastructure to increase the transparency of clinical and analytical validation.
- **Streamline and Reform the Agency’s Regulation of Manufacturers of Commercial Kits.** The FDA should initiate notice and comment rulemaking to reform the current Agency regulation of commercial diagnostic kits that are mass produced and distributed by manufacturers in order to address the extensive and well-documented concerns of manufacturers that the current FDA regulation is costly, overreaching, and so slow that some commercial kits become obsolete before they reach the market.
- **Seek Congressional Authority to Regulate Black Box Testing.** The FDA should urge Congress to confer the Agency with the authority to regulate direct-to-consumer tests and testing services where incorrect results could cause harm to patients and the test methodology is not transparent or well understood (as in the case of tests that use complex and proprietary algorithms to produce results).

Highlights of Key Concerns and Recommendations

- **The FDA Must Utilize Notice and Comment Rulemaking in Order to Issue the Proposed Framework and Notice.** To the extent it is established that the FDA has authority to regulate laboratory developed testing services, the FDA is required to issue the proposed Framework and Notification through notice and comment rulemaking as the Agency seeks to modify an existing regulation.
- **The Proposed Framework and Notification will Harm Patient Access to Standard of Care Testing Services, Innovation, and the Public Health.** While the FDA has attempted to ameliorate the negative impact of this sweeping new regulatory regime, the proposed carve-outs are not sufficient to remedy the negative impact on the ability of physicians to: provide testing services for rare diseases; sustain adequate resources to offer services where commercial kits are not available; continue the timely provision of the next generation of testing; continue to offer and improve upon newborn screening; and identify and help contain and/or treat the outbreak of infectious diseases or bio-threats.
- **The Agency Must Conduct a Comprehensive Environmental Scan to Identify Key Concerns to Target Regulatory Focus.** There is broad consensus, even among those inclined to support the FDA proposed regulation, that the Agency should conduct a comprehensive analysis of areas where regulation should be targeted and to assess future needs as well. It appears that the Agency may be concerned about a relatively small sphere of testing services and a desire to create market exclusivity through regulatory changes (that are not authorized in statute).
- **The AMA Urges the FDA to Revise the Categories of Testing Services Identified by that Agency as “Traditional,” “Rare Disease,” and “Unmet Need” Testing Services that Will Be Subject to Enforcement Discretion.** While the AMA appreciates the FDA’s effort to minimize the impact of the new regulatory requirements on patient access, the Agency is strongly urged to expand and revise these categories to protect ongoing patient access.
- **Before Finalizing the Guidance, the AMA Urges the FDA to Issue another Draft for Comment that includes Relevant Requirements and Roles of CMS, FDA, and the CDC in the Regulation of Laboratory Developed Testing Services.** Although the FDA previously reported that it would issue a draft guidance document detailing the respective roles of CMS and the FDA, and the regulatory requirements under CLIA and the FFDCA, it was not issued with the proposed Framework and proposed Notification. This has stymied efforts by the AMA and others to provide comments.
- **The AMA Urges the FDA to Exercise Full Enforcement Discretion on Low- and Moderate-Risk Laboratory Developed Testing Services and Waive the Registration, Listing, Medical Device Tax, the Unique Device Identifier Requirements for Low-, Moderate-, and High-Risk Categories.** In order to preserve the ecosystem of testing services that protects the public health and patient

access, the AMA urges the FDA to focus all regulatory oversight on testing services the Agency ultimately categorizes as high risk.

The FDA Proposal to Regulate Laboratory Developed Testing Services

On July 31, 2014, the FDA issued a Notification to Congress concerning the Agency's intent to issue the draft guidance, "Framework for Regulatory Oversight of Laboratory Developed Tests" (Framework). The Agency also issued a proposed guidance, "FDA Notification and Medical Device Reporting for Laboratory Developed Tests" (Notification Requirements). The Agency has proposed a risk-based framework for regulatory oversight of laboratory developed tests whereby these testing services would be categorized as low-, moderate-, and high-risk tests. The FDA has outlined proposed priorities for enforcing requirements that physicians and laboratories must comply with before physicians offer laboratory developed testing services to their patients (categorized by the FDA as pre-market approval requirements) and requirements that must be met after the FDA has authorized physicians to offer testing services to patients (categorized by the FDA as post-market requirements for LDTs).

High-risk Laboratory Developed Testing Services

- Registration and listing (with the option to provide notification) and adverse event reporting begin six months after the regulation is finalized.
- Premarket review requirements begin 12 months after the guidance is finalized for the highest risk devices and phase-in over 4 years for the remaining high-risk devices.
- Devices would remain on the market during review and FDA's consideration of applications.
- FDA's focus on high-risk devices begins with the following:
 - LDTs with the same intended use as a cleared or approved companion diagnostic;
 - LDTs with the same intended use as an FDA-approved Class III medical device; and
 - Certain LDTs for determining the safety or efficacy of blood or blood products.

Moderate-risk Laboratory Developed Testing Services

- Registration and listing (with the option to provide notification)
- Adverse event reporting begins six months after this guidance is finalized
- Premarket review requirements begin after the high-risk LDTs are completed, meaning 5 years after the guidance is finalized, and phase-in over 4 years
- FDA intends to utilize FDA-accredited third party review of premarket submissions as appropriate

Registration & Listing (with the "option" to provide Notification) and Adverse Event reporting for:

- Low-risk laboratory developed testing services
- Laboratory developed testing services for rare diseases
- "Traditional" laboratory developed testing services
- Laboratory developed testing services when no FDA-approved or cleared equivalent device is available--dubbed with the misnomer "Unmet Need" by the Agency

The FDA Lacks Statutory Authority and, to the Extent Authority Exists, Must Modify the Regulation through Notice and Comment

In filing comments on this proposed guidance document, the AMA does not waive its legal claim that the FDA lacks the statutory authority to regulate laboratory developed testing services. The AMA incorporates by reference the legal arguments advanced by former Solicitor General Paul D. Clement and Laurence H. Tribe in the white paper, *Laboratory Testing Services, As the Practice of Medicine, Cannot be Regulated As Medical Devices* (Clements & Tribe Analysis), attached hereto. Furthermore, to the extent that it is established that the FDA does have such authority, the overwhelming weight of legal authority dictates that the proposed new requirements for laboratories outlined in the Framework and Notice documents must be issued through notice and comment rulemaking. Nothing in these comments is intended to waive or impact adversely in any way the AMA's ability, alone or in combination with other stakeholders, to pursue separate comments, litigation, or other remedies with respect to the proposed regulatory framework or related issues.

The Clinical Laboratory Improvement Amendments (CLIA)

For decades, the conditions under which laboratory developed testing services are offered have been extensively regulated under a comprehensive, interlocking framework of federal laws, state laws, and peer review "deemed" authorities.

The federal law governing laboratories where these services and procedures are offered has been the CLIA. CLIA establishes the requirements governing the operation of clinical laboratories to ensure the safe and accurate function of laboratories and the testing services they provide. These requirements cover:

- the laboratories themselves;
- the necessary certifications for laboratory personnel from pathologists and geneticists to technicians; and
- the documentation of procedures for individual clinical laboratory tests.

In addition, laboratories are subject to inspections under both CLIA and state law.

Laboratories where moderate- and high-complexity tests are performed can choose to submit to additional oversight through deemed peer review authorities, such as the College of American Pathologists (CAP), the Joint Commission, and others, which add additional expertise in reviewing both the operation of the laboratory and the analytical and clinical validity of individual tests. **This additional**

oversight of laboratories where moderate- and high-complexity tests are performed also involves the use of proficiency testing to ensure the accuracy of testing results (analytical validity).

The AMA agrees with other major stakeholders that this comprehensive yet flexible oversight framework has produced some of the most significant advances in medicine to occur in the last century—powered by physicians engaged in the practice of medicine helping their patients, many of whom have traveled painful and long diagnostic journeys. This flexibility has ensured that thousands of tests are offered to meet a wide-range of diverse and varied patient needs, which is in sharp and marked contrast to the small number of commercial, mass produced test kits that have been cleared or approved by the FDA.

To the extent that stakeholders have expressed concerns with certain types of testing services or lack of transparency vis-à-vis clinical and analytical validation, the most appropriate course of action would be for CMS to exercise its statutory authority to modernize CLIA oversight. **The AMA has already urged Congress to direct CMS to modernize CLIA, by mandating third-party accreditation in all laboratories where moderate- and high- complexity tests are performed.** While CMS-CLIA has elected to limit its oversight obligations, this is not adequate justification for FDA action. However attractive it would be for the FDA to assume CMS’ obligations to provide oversight, it is not statutorily authorized and is ill-advised given that it will undermine access to a wide range of testing services and undermine patient care, public health, and innovation.

Federal Food, Drug and Cosmetic Act

Physician services are not devices and cannot be shoehorned into the Federal Food, Drug, and Cosmetic Act (FFDCA) for purposes of regulating the practice of medicine. This is detailed in the *Clements & Tribe Analysis*. Furthermore, as outlined below, the differences between commercial diagnostic kits and laboratory developed testing services underscore the obvious distinctions. In addition, the legal, clinical, and practical problems raised by the Agency asserting the legal fiction that physician services and procedures are devices is further demonstrated by the device labeling requirements and prohibitions on off-label promotion of the FFDCA. However, if the Agency moves forward, the AMA offers recommendations below to ameliorate the negative impact on patient access to standard-of-care laboratory services and innovation that drives continual improvement to patient care.

Practice of Medicine Distinct from Manufacturer of Commercial Kits

There is fundamentally and undisputedly a legal and material difference between the practice of medicine (which laboratory developed testing services are) and mass produced commercial kits that are shipped by manufacturers around the nation. The differences are summarized in Figure 1 on the next page.

Laboratory developed testing services are procedures developed and performed by physicians and the laboratory professionals they oversee for specific patients, equivalent to a surgeon and his or her surgical team that perform surgeries on a specific patient. A physician practicing laboratory medicine will utilize reagents (products that are often subject to FDA regulation) and instruments (which may or

may not be FDA regulated) when conducting testing, but the laboratory testing services are the technical expertise and clinical judgment of a physician who develops and validates the test performed under testing conditions that are already subject to oversight under CLIA and often state authorities or other accreditors. The physician makes a clinical determination as to what products to utilize, what patient sample preparation is needed, and what instruments are used in order to perform the testing services. A physician who develops, validates, and performs the testing procedures is knowledgeable about and responsible for each component part and each step and procedure involved with performing the test. Unlike a commercial kit, the physician's services cannot be packaged and shipped to multiple laboratories.

Figure 1. Fundamental differences between laboratory developed testing services and commercial kits.

Critical distinctions exist between laboratory developed testing services and commercial diagnostic kits

Commercial diagnostic kits are an actual product that can be packaged, labeled, and **shipped in interstate commerce to numerous laboratories**, in contrast to the services and procedures offered by a physician in a **single laboratory as part of his or her practice of medicine**.

Once the manufacturer distributes the commercial diagnostic kits, the **manufacturer no longer retains control** over how the test is conducted, what patient is tested, and how the information is shared with the treating physician, whereas **physicians retain control and decision-making authority** throughout the continuum from design to delivery of test results.

Physicians who utilize a **commercial diagnostic kit are not able to evaluate the underlying methods and components of the commercial kit**. In contrast, when offering laboratory developed testing services **physicians have a complete understanding** of the results as well as the underlying methods, sample preparation, inputs, procedures, and validation of the test. This markedly improves patient safety by allowing for recognition of false-positive and false-negative results.

A commercial diagnostic kit is a packaged product that is **engineered** to be performed **anywhere** for a **patient within the validated population**. It **cannot be altered for specific patient needs**. In contrast, **laboratory developed testing services are developed by physicians for specific patients** based on their clinical condition and in consultation with the patient's treating physician, and can be improved or altered to fit individual patient needs.

Real Life Implications for Patients

I had a 57 year old male patient with lung cancer who had received multiple lines of therapy prior to testing. A rearrangement in the gene encoding ALK drives tumor growth in a subset of lung cancers. The only sample type available for testing from my patient's tumor was a cytopathology specimen, which is not an approved specimen type for the existing FDA approved

companion diagnostic for the drug crizotinib, an ALK inhibitor that can induce tumor regression in ALK-positive tumors. We were able to test the sample for ALK rearrangement because of adaptations we made to the assay to allow us to test this specimen type. Our patient was positive for the ALK rearrangement and was put on crizotinib; and the disease has been controlled for over 2 years. Under the FDA draft guidance, we would have to submit this adaptation for approval prior to offering it, delaying this patient's time to a result. With the aggressive nature of lung cancer, there is a good possibility that without a targeted therapy, the patient would be deceased within 6 months, which may be less time than the FDA approval process takes.

Oversight and responsibility for the design, development, validation, monitoring, and reporting attendant to laboratory developed testing services constitute the practice of medicine. These are within the scope of a physician's practice and physicians have a legal responsibility for them. In contrast, with commercial diagnostic kits, the design, development, and manufacturing are physically and distinctly separate from the laboratory operations, including sign-out of tests (meaning the reporting, record review, and other components of communication with treating physician colleagues). With laboratory developed testing services, the physician practice components of design, development, monitoring, and application to clinical care are inseparable and inextricably linked.

Laboratory medicine is a defined field of medicine. The practice of laboratory medicine is a recognized subspecialty within the practice of medicine, as demonstrated by the existence of separate medical departments devoted to this specialty, and training programs for which the successful completion of medical training is a pre-requisite. This complex medical specialty is its own specialty for a host of reasons, including that very few tests are as simple as "put sample in, get result out." An understanding of the nuances of laboratory testing, as applied to medical practice, is laboratory medicine. In order to offer these medical services to patients, physicians practicing laboratory medicine have completed post-graduate medical training and passed board-certification examinations administered by the American Board of Pathology or the American Board of Medical Genetics and Genomics. Physicians continue to maintain certification under the American Board of Medical Specialties, are licensed by state medical boards, and pay for and are covered by medical malpractice insurance.

Real Life Implications for Patients

After obtaining my medical degree and completing a residency in medical genetics, I trained for an additional two years and obtained board certification in clinical molecular genetics from the American Board of Medical Genetics and Genomics. I have almost 20 years experience as a practicing geneticist developing and performing clinical laboratory testing services. I actively maintain my certification by reviewing literature, writing papers, attending seminars and conferences as a part of my professional development. I understand that some are pushing the FDA to regulate individuals like myself as manufacturers when rendering clinical decisions. This is nonsensical. Laboratory service is part of the practice of medicine. Where professional judgment is used to diagnose and determine a treatment course for a patient, I work in concert with healthcare professionals to determine the appropriate method and test. I am not a "robot"

that automatically sends a result regardless of whether the testing is appropriate or not. I continually try to improve my tests and their performance through analytical validation and clinical evidence. Patients are at the center of everything that I do.

Labeling Services and Prohibitions on Discussing Medical Options

For commercial diagnostic kits, the components of the kit are obviously medical devices subject to regulation; the engineered copies of the test kit also are a product and the process of labeling the device and component parts straightforward. The draft guidance does not specify what should be labeled in the context of laboratory developed testing services even though this is an essential element of compliance under the FDCA. The FDCA sections 201(k)-(m) provide:

(k) The term “label” means a display of written, printed, or graphic matter upon the immediate container of any article; and a requirement made by or under authority of this Act that any word, statement, or other information appear on the label shall not be considered to be complied with unless such word, statement, or other information also appears on the outside container or wrapper, if any there be, of the retail package of such article, or is easily legible through the outside container or wrapper.

(l) The term “immediate container” does not include package liners.

(m) The term “labeling” means all labels and other written, printed, or graphic matters (1) upon any article or any of its containers or wrappers, or (2) accompanying such article.

There are no obvious places to put a label on the procedures and services offered by physicians. The physician’s knowledge and skills, quite obviously, could not be labeled.

Furthermore, even to the extent that the FDA proposes to define laboratory developed testing services as something other than what they are—physician expertise and procedures—the Agency’s application of these provisions to physicians would create liability for off-label use and “promotion” for physicians. Currently, when physicians determine that a product labeled for a specific intended purpose has an alternative beneficial clinical use, they are permitted to use the product for an “off-label” purpose and are permitted to discuss such use with other physicians. Although there remains an ongoing legal dispute between the FDA and drug, biological, and device manufacturers regarding off-label promotion, manufacturers are generally prohibited from promoting off-label uses and face significant sanctions if and when the Agency can establish that the manufacturer has “misbranded” the product.

Physicians, in contrast, are permitted to inform patients and other physicians when a commercial diagnostic kit, labeled for one purpose, has a clinical benefit for another purpose. This is the very definition of medicine, i.e., a physician using his or her clinical expertise to appropriately diagnose and treat a patient who may require care that is not “one-size fits all.” Competent and quality medical care rests on physicians’ discretion and responsibility to treat patients in a manner that meets each patient’s

individual needs. Removing a physician's ability to practice medicine off-label will jeopardize patient access to medically necessary and potentially lifesaving treatment.

Real Life Implications for Patients

An oncologist at my medical center requested that our laboratory, directed by myself, a board-certified molecular pathologist, assess a formalin-fixed paraffin embedded tissue sample from recently-diagnosed papillary thyroid carcinoma. The oncologist was aware that 30-50% of papillary thyroid carcinomas contain the BRAF V600E mutation. Since carcinomas carrying the V600E variant are responsive to several drugs (vemurafenib, dabrafenib, trametinib), the oncologist wanted to find out whether his patient may be a candidate for one of the drugs. The FDA-approved BRAF V600E test kit is intended only for testing melanoma, not thyroid carcinomas. However, using my expertise as a molecular pathologist, I made modifications to the FDA-approved kit so that I could detect the BRAF variant in thyroid carcinoma cells. The patient's thyroid carcinoma tested positive for the presence of the V600E variant, an indication that she was a candidate for drugs targeting BRAF V600E. Her oncologist prescribed dabrafenib, and the growth of her tumor has slowed dramatically.

Use of the FDA-approved BRAF V600E kit on any tissue other than melanoma is considered a modification to the intended use, i.e., an off-label use, making it a laboratory developed testing service. As a physician, I need to use every tool available and appropriate to treat my patients. I would have failed my patient if I had not practiced the best medicine possible by testing her thyroid carcinoma for the presence of the V600E variant. Importantly, if the FDA had required that I obtain its approval to use the FDA-approved BRAF V600E test on a tissue for which it was not approved, my patient would have experienced an unacceptable delay in her care that could have severely affected her chances of survival.

A prohibition on discussing testing options with patients and treating physicians including off-label uses would prevent physicians from meeting both ethical and legal obligations. Furthermore, not only are physicians permitted to discuss off-label uses of devices, drugs, and biologicals, but this is at the heart of innovation. In the course of providing care to patients, physicians are able to identify emerging previously unknown patterns, symptoms, and outcomes that were not otherwise contemplated when a method, approach to medical care, procedure, device, drug, or biological was initially devised for patient care. **If the Agency proceeds with finalizing the guidance, the AMA recommends that the FDA establish a safe harbor carve-out for off-label use and promotion in the context of laboratory developed testing services for physicians.**

Finally, the ability of physicians to offer their patients the testing services they need based on the rapidly acquired and clinically validated genetic and genomic knowledge unlocked by the Human Genome Project and subsequent reductions in sequencing costs will come to a halt unless the FDA reduces the financial cost and resources needed to prepare a submission for FDA clearance or approval. FDA approval is costly and time-consuming even for large corporations often singularly focused on a very

small sliver of the universe of tests patients need daily. If FDA clearance or approval is required once a manufacturer commercializes a product, all versions of the test including superior versions would most likely cease given the cost and resource barriers. **We strongly urge that where clinical validity is demonstrated by a similar commercial high risk test, physicians and clinical laboratories seeking approval should not be required to re-demonstrate this via costly pre-market approval (PMA) submission. We strongly urge that the FDA allow laboratory developed testing services categorized by Agency as high risk to be compared to high-risk approved devices as predicates.**

Rulemaking Required for Legal Reasons and to Prevent Disruption to Care

While the AMA does not waive our legal claim that the FDA lacks the statutory authority to regulate laboratory developed testing services, to the extent that it is established that the FDA does have such authority, the overwhelming weight of legal authority dictates that the proposed new requirements outlined in the draft guidance must be issued through notice and comment rulemaking. The Federal Administrative Procedures Act (APA) establishes a simple procedure for rulemaking so that interested parties are given an opportunity to participate in the rulemaking through submission of written data, views, or arguments. Notice and comment will increase the likelihood that the agency will be able to achieve regulatory goals without jeopardizing the current delivery of testing services to patients and the continued advancement in testing and patient care.

Should the Agency finalize the guidance documents, the guidance would conflict with the express language of 21 C.F.R. § 807.65(i), which specifically exempts clinical laboratories from device registration requirements. Because section 807.65(i) was issued through the notice and comment rulemaking process, the regulations are legislative rules. In order to revoke this exemption, the FDA must amend this regulation through notice and comment rulemaking. It appears that the Agency has attempted to side-step this by providing laboratories the option to provide notification in lieu of registration, which is non-availing since the notification requirements are far more extensive (and therefore onerous) than the registration requirements. Failure to comply with the notification requirement will trigger the registration requirements and associated compliance obligations that are costly and particularly challenging for laboratories and physicians to meet.

Aside from the FDA's legal obligation to proceed through notice and comment rulemaking, the FDA's compliance with the APA would provide essential protections for the regulated to ensure that subsequent changes are promulgated with notice and in a deliberate, informed manner consistent with law. Protections afforded by the notice and comment rulemaking process include the requirement that the Agency respond to all stakeholder comments and undertake an economic impact analysis of the new regulatory oversight to assess the estimated burden on the regulated. The foregoing are critical exercises to address widely-held concerns with the lack of specificity and clarity in the proposed guidance that undermine the ability of impacted stakeholders to provide constructive and informed feedback on the proposed changes. Finally, guidance documents do not carry the legal certainty and weight of regulations that provide the regulated reasonable assurances and ability to comply with the FDA's requirements.

Proposed Regulation Will Undermine Patient Access to Standard of Care Testing, Innovation, and Public Health

Ethical Obligations of Physicians to Their Patients

Physicians have been and continue to be at the forefront of the intersection of providing patients' medical care and advancing clinical knowledge to improve upon the current standard of care. Physicians are unique stakeholders who have both an ethical and legal obligation to each individual patient to whom they render medical care. The first directive of physicians is to do no harm and to advance the interest of their patients to whom they provide medical services. While there are important interested stakeholders, including manufacturers focused on commercializing innovations, insurers focused on lowering costs, and regulators tasked broadly with safety, physicians have a direct relationship with patients and an obligation to provide medical services that meet patient specific clinical needs; these are services physicians have provided for decades in the context of laboratory developed testing services.

Physicians are not motivated to offer testing services in the same manner as a manufacturer is motivated to sell a commercial product. Instead, as new clinical knowledge emerges in the course of clinical research or providing direct patient care, physicians practicing laboratory medicine have been at the forefront of sharing such information for third-party review and validation to advance their patient's care and the care of patients around the nation. The FDA's proposed regulation of laboratory developed testing services will have a sweeping and widespread negative impact on patient access to established testing services representing the standard of care. The proposed regulation will also leave the country vulnerable to bio-threats, outbreaks of infectious diseases, and undermine other important public health objectives such as widespread and accessible newborn screening.

Proposal Undermines Patient Access to Standard of Care Testing and Innovation

The Agency's proposed action will:

- Reduce the number of testing services that physicians are able to offer and the laboratories where these services are performed.
- Undermine efforts to maintain laboratory resources needed to offer new laboratory testing services because of the potentially short duration of time in which the tests could be offered. As a result, laboratories will drastically reduce their services or close altogether, and fewer physicians with the training and expertise to offer these services will be employed by the remaining laboratories.
- Stop or dramatically slow the ground-breaking innovations developed by physicians as part of their clinical practice of laboratory medicine—innovation that is the genesis of commercial test kits and a key part of a physician's ability to properly diagnose and treat patients.

At the same time that the FDA's regulation will erect additional impediments to medical advancement in the U.S., it will contribute to increased costs associated with (1) poor patient outcomes given decreased access, and (2) increases in per test costs because of limited competition.

Proposal Threatens Public Health

For a number of reasons, this proposed regulation heightens public health related concerns, and the AMA strongly urges the FDA to fully evaluate, assess, and seek public comment on this issue before proceeding further.

Neither the FDA nor CMS have adequately taken into consideration the threat to public health posed by the actions of the FDA (through this proposal to regulate physician testing services and procedures) and CMS (through Medicare coverage policy)—policies that will restrict access to laboratory developed testing services representing the standard of care. Both agencies have stated that they are not charged with considering the implications of their policies that would, when combined, dramatically shrink the availability of laboratory testing services—as both federal agencies have stated that they are not charged with ensuring adequate access to testing services for individual patients. This is incorrect, and underscores the urgent need for the U.S. Department of Health & Human Services (HHS) to convene the CDC, FDA, and CMS to more fully evaluate HHS strategies to protect the nation from infectious disease outbreaks and bio-threats in an open and rigorous discussion with the major stakeholders as well as address the capacity to advance other public health priorities such as newborn screening.

Our concerns have only deepened following testimony offered during the FDA's two-day workshop on January 8th and 9th, 2015, by public health officials from the State of Georgia (concerning the impact on newborn screening) and the State of Texas (concerning infectious diseases). These concerns have been outlined in detail as part of the Association of Public Health Laboratories (APHL) submission to the FDA docket. In addition to the concerns and points highlighted in the APHL comments, the FDA proposed regulation does not adequately account for the impact on public health laboratories nor does it provide consideration for the essential role of the sentinel network of clinical laboratories across the nation that provide extended reach for public health laboratories. In addition to sentinel laboratories, clinical laboratories around the nation provide surge capacity in the context of bio-threat or infectious disease outbreaks. Furthermore, as noted by clinicians in public health laboratories, the proposed framework will put undue burden on the public health system, which includes laboratory testing for diagnosis, screening, outbreak investigation and surveillance, and as currently drafted, the regulation will have the potential to greatly reduce or eliminate testing that provides important public health benefits.

Summary

There are opportunities for the FDA to advance the consensus goal of improvement to clinical testing services and procedures without regulatory overreach that poses a threat to patient access to essential testing services, undermines public health, and impedes the continual medical practice improvements that have led to rapid application of clinically relevant discovery to medical practice.

FDA Rationale for Issuing Draft Guidance Conclusory & Lacks Specificity

The FDA Must Conduct and Issue for Public Comment a Landscape Analysis

A number of commenters at the FDA Workshop noted that the FDA has not adequately identified the scope of its concern to justify the sea change sought in regulation. The AMA is very concerned that patient access to well-established, standard of care testing services provided by physicians to millions of patients each year will no longer be available once the FDA finalizes its proposed regulation of laboratory developed testing services.

Though there are many unanswered questions raised by the FDA's proposal, it is already clear that the proposed guidance would impose new, costly, and burdensome requirements on even low- and moderate-complexity testing services. More troubling, the Agency has repeatedly acknowledged that it does not know the number of times these testing services are offered or the universe of services being offered by physicians that would be subject to this regulation, while at the same time claiming that adequate Agency capacity exists to regulate such physician services. Many of these testing services, along with those that potentially will be categorized as high-risk by the Agency, have represented the standard of care for years.

As a threshold matter, the FDA has offered little to no evidence that patients have suffered harm on a persistent or widespread basis justifying the imposition of broad new and costly regulatory requirements that will prevent patients from obtaining needed testing services. The resulting access problem certainly will harm patients. When queried as to what problem the FDA is addressing and any corresponding documented patient harm, the Agency has declined to identify the number of testing services and patients that the FDA has identified, tracked, or obtained from literature or media accounts.

The AMA urges the FDA to define and identify the problem(s) and the breadth thereof, and share such an analysis with stakeholders, before proceeding with any plan to implement oversight. The FDA appears to have conflated one problem—lack of incentives to seek FDA approval/clearance—with a poorly articulated statement of patient harm vis-à-vis laboratory developed testing services.

Proposed Regulation is Sweeping in Scope though the FDA's Concerns Appear Centered on Small Universe of Testing Services and Certain Provider Types

The FDA's concern, though not explicitly stated, appears to involve highly complex genetic/genomic tests. The AMA agrees that a small subset of complex genetic/genomic tests, e.g., those that use proprietary and non-transparent algorithms that do not lend themselves to review and refinement by laboratory physicians and professionals, should be subject to oversight, potentially by the FDA. The

AMA supports an oversight mechanism that would ensure the analytical and clinical validity of such tests. However, the Agency's proposed framework goes far beyond addressing those "black-box" tests, and instead subjects a massive number of laboratory developed testing services to costly and burdensome requirements that would add little or no value to the testing services but would severely disrupt their availability to patients and treating physicians.

FDA Lacks Capacity to Regulate in this Space

While the President outlined a vision for accelerating Precision Medicine in the 2015 State of the Union, the proposal reportedly hinges on new and substantial funding to support National Institutes of Health research and additional funding to support FDA regulation of diagnostic testing. However, additional funding alone will not be sufficient to address the capacity challenges currently faced by the FDA and the very modest number of commercial diagnostic kits cleared or approved by the Agency. **It is incumbent on the Agency to identify for industry, physicians, and patients how it plans to expand its capacity.**

Manufacturers face commercialization challenges largely because of the burdensome, opaque, and lengthy FDA clearance and approval process. A recently issued independent analysis of the FDA's 510(k) review times belies the FDA's published statistics on the topic. In a December 2014 study by the Medical Device and Diagnostic Industry (MDDI)¹, 510(k) review time data from FDA's publicly available database were analyzed. The conclusions include the following:

- Use of the third-party review program has significantly declined, while the review times for 510(k)s have increased.
- There is no review-time advantage to submitting an Abbreviated 510(k) compared to a Traditional 510(k).
- Even those devices most frequently reviewed by FDA still saw an increase in their overall review times between 2008 and 2012.

The foregoing data analysis is only half the story. The Agency's performance on review times for commercial diagnostic kits includes:

- Commercial diagnostic kit 510(k)s take significantly longer to review than 510(k)s for other types of devices.
- Between 2008 and 2012, the average review time for an IVD 510(k) was 183 days compared to a non-IVD 510(k) which was 127 days.

As noted by the authors of the article, the above findings are of particular importance given the FDA's proposed plan to regulate laboratory developed testing services. Reportedly, the same FDA staff reviewing commercial diagnostic kits will review laboratory developed testing services. While the President's Precision Medicine initiative may seek from Congress substantially more appropriations to expand the FDA's capacity to rapidly review and approve new tests, understandable concern remains

¹ Medical Device and Diagnostic Industry. 510(k) Statistical Patterns. <http://www.mddionline.com/article/510k-statistical-patterns-12-02-2014>

that FDA review of commercial kits will be further slowed once it begins regulation of physician laboratory developed services.

The landscape analysis that the AMA and other stakeholders have urged will assist in prioritizing what are clearly limited resources toward the tests that pose the highest risk to patients and that are not validated through a peer review process. By focusing the Agency's resources, it is more likely that the Agency will enjoy strong consensus support from the medical community.

Although the FDA has proposed a nearly 10-year window for phasing-in FDA's regulation of all laboratory developed testing services (including a large number that are not genetic or genomic tests), the upfront disruption that will be precipitated by the notification requirements alone will divert already limited Agency and health care system resources away from developing a workable regulatory framework to address the manufacturing challenges associated with technologies that are rapidly entering patient care and replacing current or older technologies, such as next generation sequencing, whole genome/exome sequencing, and associated testing. The technical and clinical expertise that will be required to develop a framework for these new technologies, implement such a framework, and monitor compliance will be significant. The FDA's approach to the oversight of laboratory developed testing services—creating a highly complex and rigid regulatory framework when the field is undergoing seismic changes that will bring ground-breaking testing and treatment advances—is at odds with the goal of ushering in a new era of patient access to high quality tests and treatments. **While the AMA generally supports the phased in approach to compliance given the significant risk posed by rapid implementation to patient care, the guidance does not address the new next generation technologies that will almost certainly be deployed in the meantime. An explicit discussion of the interplay and engagement with the physician community is strongly urged.**

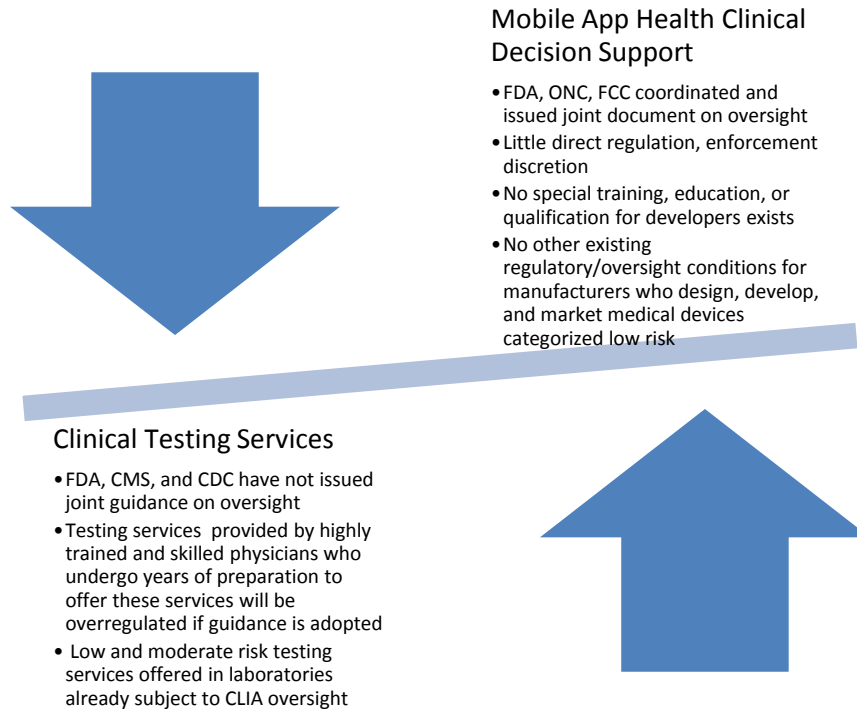
The FDA Must Coordinate and Issue Guidance and Regulation with CMS and the CDC

The AMA strongly urges the FDA to consider the compelling need to avoid duplicative and confusing regulation and oversight by two federal agencies, a number of states, and accreditation bodies. In a 2011 FDA meeting regarding the reauthorization of Medical Device User Fee Amendments (MDUFA), an Agency representative stated that a “risk-based, phased-in approach” toward regulation was under consideration and that three guidance documents coming out together would detail the proposed road forward in oversight of laboratory developed testing services. Reportedly, one of the documents would outline the differences and similarities between CLIA regulations and the FDA’s Quality System Regulations (QSRs). **The FDA’s draft guidance does not provide any meaningful or discernable detail adequate or sufficient to ascertain where CLIA requirements end and where the FDA requirements begin.**

The AMA has asked the Agency for this information and months have passed without a response. The FDA has proposed a framework for regulation of services and procedures, but has not clarified nor produced any documentation of coordination with CMS based on this new proposal. Furthermore, the FDA has been silent as to the role of the CDC vis-à-vis CLIA and the new FDA requirements. (CDC, in partnership with CMS and FDA, supports the CLIA program and clinical laboratory quality.) Congress charged the FDA, the Federal Communications Commission (FCC), and the HHS Office of the National Coordinator for Health Information Technology (ONC) to jointly develop a proposed regulatory framework for digital health to avoid duplicative and burdensome regulation. **There is similarly an urgent need for, at a minimum, CMS, CDC, and FDA to engage major stakeholders in a transparent process and propose a framework that clearly and specifically identifies areas where the agencies will avoid contradictory, overlapping, and or/and ambiguous oversight parameters.**

It should be noted that the Agency’s coordination with the FCC and ONC has been strongly supported by major stakeholders and a similarly holistic approach is needed in this area. The AMA also notes—as an engaged stakeholder in the discussions around digital health regulation and the FDA’s proposal to regulate laboratory developed testing services—that the FDA’s approach to patient/consumer safety is neither consistent nor coherent when contrasted with the relatively laissez-faire approach adopted for mobile health applications that the Agency considers medical devices (Figure 2). It is perplexing that the FDA is exercising enforcement authority over mobile applications it has categorized as “low-risk” medical devices even though there is no other agency providing oversight to ensure that the devices work, no learned intermediary to ensure the device is being used properly, and no existing standards or requirements related to proper function of the device or clinical relevance—which makes the Agency’s position relative to professional services and procedures offered by highly trained physicians in regulated laboratories all the more incongruous.

Figure 2. Mobile App Health Clinical Decision Support vs. Clinical Testing Services



The FDA has taken markedly different regulatory approaches to certain clinical decision support mobile apps that the Agency has categorized as low risk medical devices that will not be subject to direct regulation and may lack learned intermediaries for use as compared to physician laboratory developed testing services, which are offered under regulated conditions by experienced and highly trained medical professionals.

CLIA Provides Superior Processes to Identify Testing Errors

An underlying, occasionally explicit, concern has been voiced that laboratory developed testing services produce incorrect results that lead to patient harm. A recurring, but extremely limited, number of examples have been provided in light of the millions of laboratory developed testing services performed every year. Furthermore, these very concerns prompted the passage of CLIA in order to provide ongoing, active monitoring of a host of factors that could contribute to test failure and patient harm. Under CLIA, physicians and the clinical laboratories where they provide these services are already subject to ongoing quality assurance and improvement activities that would identify far less serious test “failures” in an immediate, reliable, and ongoing manner.

Real Life Examples for Patients

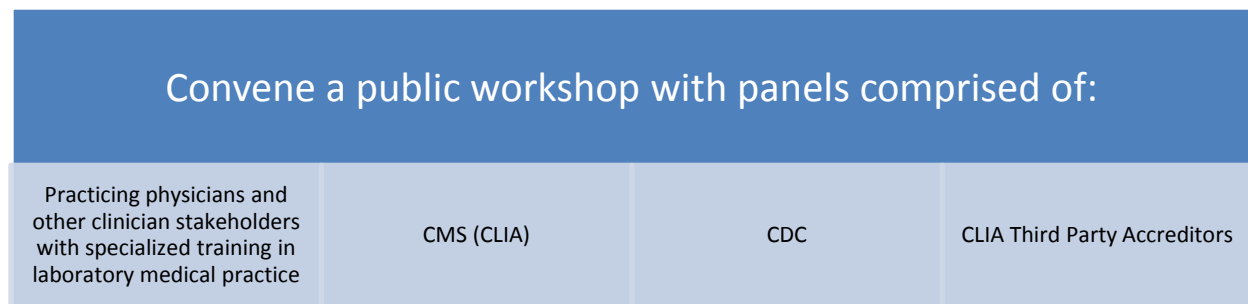
A patient needed testing for the ALK rearrangement that is present in a subset of lung cancers. Our laboratory evaluated the patient’s tumor specimen using the FDA-approved kit and the established scoring criteria included in the FDA approved package insert. The specimen was classified as ALK-negative based on these criteria, however we recognized that the pattern was not typical of that seen in most specimens. We considered the possibility that there was, in fact, an underlying rearrangement that was poorly detected based on existing criteria but that our laboratory detected based on careful observation. Based on this observation, I (the physician director of the laboratory) discussed the unusual findings with the patient’s treating physician and recommended that additional testing, using another methodology, be performed. Using two other methods for ALK testing, the specimen was found to be positive for the rearrangement. The patient was treated with crizotinib and responded to therapy. This is another example of the strict ‘lock in’ of assays as imposed by FDA approval that inhibits the practice of medicine and reduces the ability of laboratory physicians to carry out their duty to impart the best possible care for their patients.

Not surprisingly, the FDA’s adverse event report requirement would only capture the most extreme situations—unlike CLIA, which is ongoing and far more nuanced—so much so that many laboratories have stated that it would be rare that a testing failure would cause or contribute to a death or serious injury as defined by FDA regulations because of the ongoing quality improvement processes and the nature of medical practice. Yet, compliance with the Manufacturer Reporting Requirements involves the development of policies and procedures for reporting adverse events as well as an infrastructure to analyze potential adverse events, including maintenance of protocols for investigations and analyses that would siphon limited resources away from providing patient services. CLIA provides an ongoing set of processes to address analytical validity (and any associated process failures that would produce a faulty result). **At most, the FDA should limit enforcement of the Manufacturer Reporting Requirement**

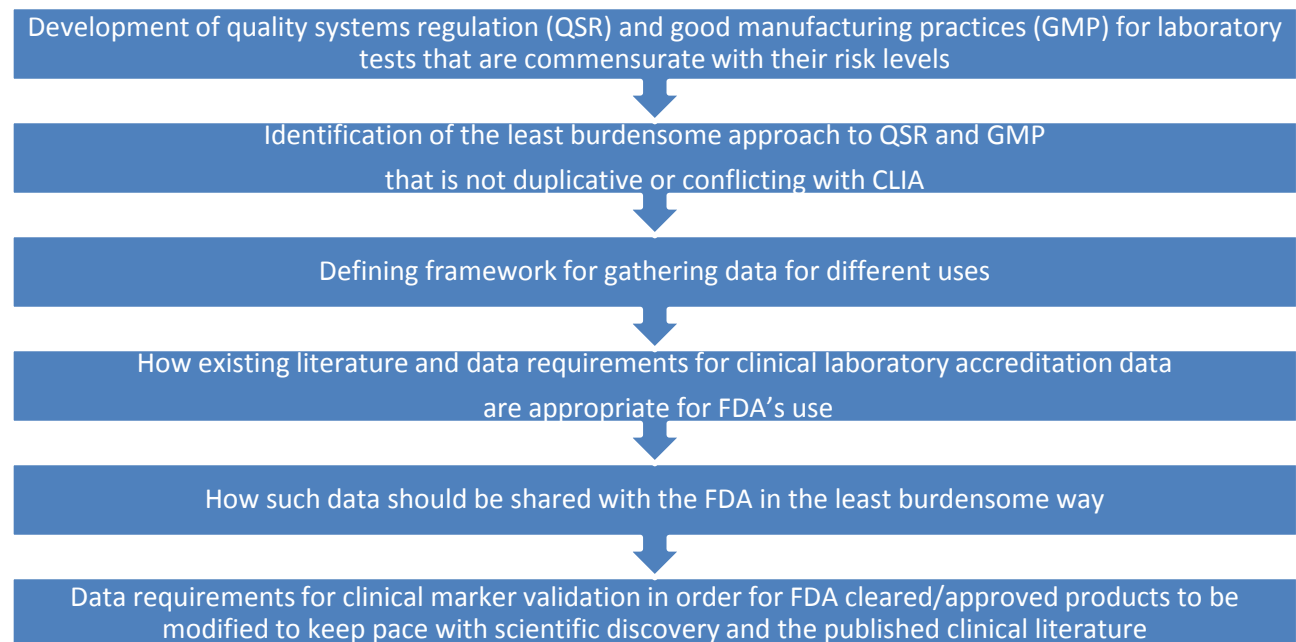
to those laboratory developed tests most likely to present serious risk to patients, namely those for which premarket approval has been required.

Process Considerations

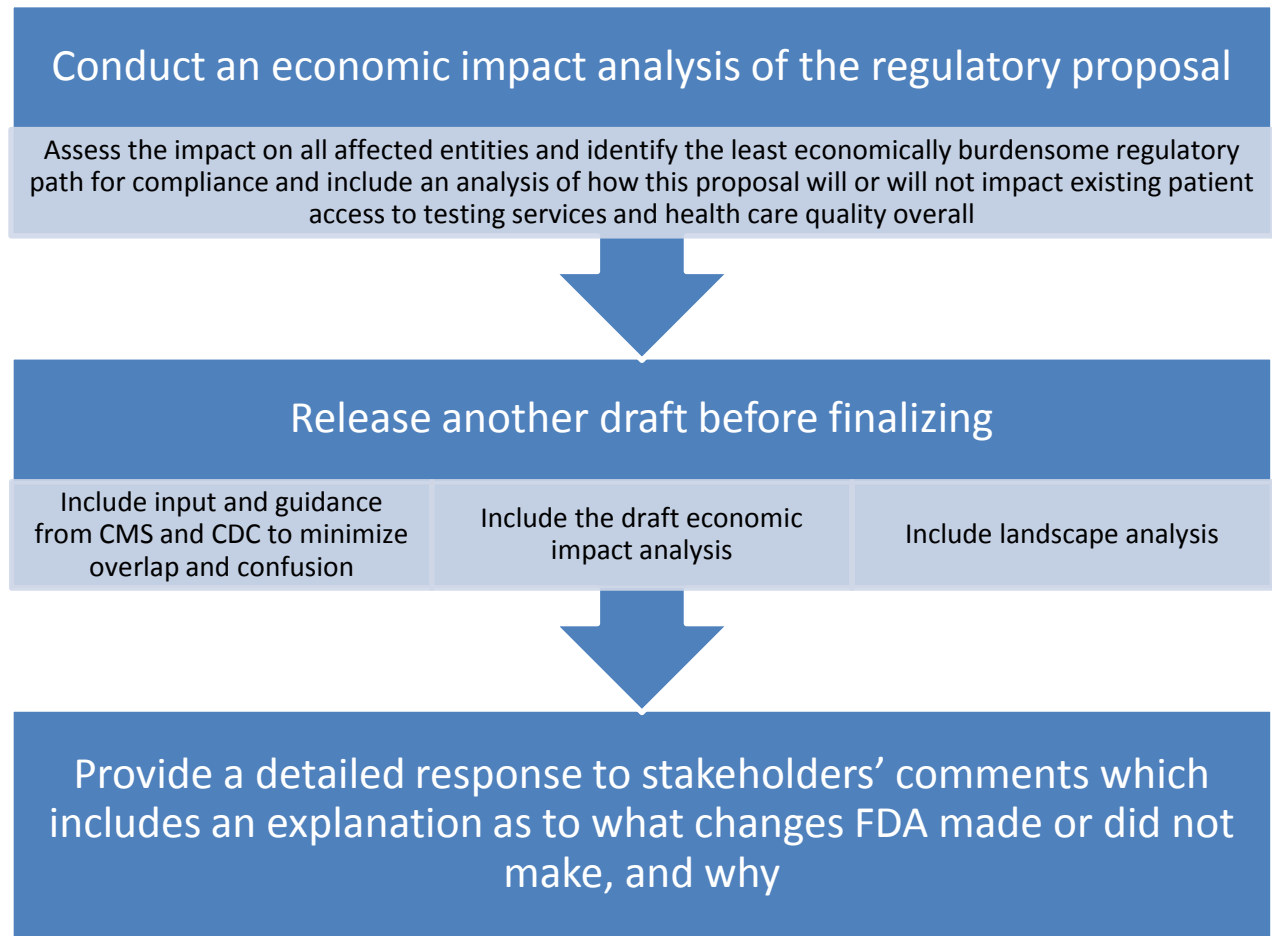
The AMA has a number of process related recommendations to the extent the FDA’s statutory authority to regulate is upheld and notice and comment is not required. **First, since the entire Framework is dependent on risk classification, the FDA should undertake a process to define the criteria it will use for risk classification before the guidance is finalized.** To subject physicians and laboratories to regulatory requirements based on risk categorization without clearly defining those categories does not provide sufficient information on what steps need to be taken in order to comply with the guidance. In addition, the AMA urges the FDA to:



While the AMA applauds the FDA’s decision to conduct a public workshop and include a diverse cross-section of panel participants, there remain largely technical questions and issues on which the FDA would benefit from subject matter expertise including from sister agencies. The FDA should seek input on the following:



Thereafter, the AMA urges the FDA to:



Proposed Carve Outs Not Adequate

The AMA appreciates the attempt to identify tests for which the FDA will exercise enforcement discretion to varying degrees. However, the exemption criteria are far too limited, would result in an unacceptable disruption to patient access, evince a lack of understanding for the critical needs met by laboratory developed testing services, and are not analytically consistent with a risk-based approach. These shortcomings are driven in part by an overly restrictive definition of a laboratory developed test that fails to recognize the modern nature of the health care system designed to serve and provide access to patients of all needs and in any geographic location.

FDA Definition of a Laboratory Developed Test

For several reasons, the definition of a laboratory developed test set forth in the draft guidance, i.e., “an IVD that is intended for clinical use and designed, manufactured and used within a single laboratory,” is not applicable to or workable within the context of modern laboratory medicine. First, laboratory physicians and professionals are not manufacturers, and therefore laboratory developed testing services are not “manufactured” in their laboratories, as the definition in the guidance implies. Second, laboratory developed testing services are not “devices.” (Furthermore, there is a legal dispute whether the scope of what the FDA regulates as “*in vitro* diagnostics” *in toto* constitutes a medical device under the FDCA.)

Third, to reach a large number of patients and provide critical services across wide geographic locations, modern health systems quite often include several laboratory locations, many of which hold separate CLIA licenses. However, separate location and license does not mean separate entities. Laboratory physicians and professionals within the same health system share protocols and expertise and routinely collaborate to develop and optimize tests that serve their patients at separate locations. The use of a laboratory developed testing service that has been validated and optimized to perform at several locations within a health system is still a laboratory developed testing service. The true characteristics of the service are still present: a physician (or team of physicians) has made a clinical determination as to what products should be utilized, what sample preparation is needed, and what instrumentation should be used to perform the service. That the service performs with optimal analytic and clinical validity under the expertise of physicians in more than one laboratory location within a health system should not disqualify it as a laboratory developed testing service.

For the aforementioned reasons, the AMA urges the Agency to alter its definition of a laboratory developed test to “a test that is developed, validated and used for planning or implementing patient care, and is intended for use only by the health system in which it was developed.” Health system should include reference laboratories that have an established obligation to provide testing services that are not available within the health system.

Enforcement Discretion for Traditional Laboratory Developed Testing Services

The AMA is pleased that the Agency has proposed to continue enforcement discretion for those laboratory developed testing services it refers to as “traditional LDTs.” However, we find the “traditional LDT” criteria set forth by the Agency to be both unclear and unnecessarily restrictive. Our concerns about Criterion (1), “whether the device meets the definition LDT in this guidance,” are outlined above in the discussion about the definition of a laboratory developed test.

Criterion (2), “whether the LDT is both manufactured and used by a health care facility laboratory (such as one located in a hospital or clinic) for a patient that is being diagnosed and/or treated at that same health care facility or within the facility’s health care system,” again inaccurately implies that laboratory physicians are manufacturers. Most troubling, however, is that this criterion implies that a laboratory developed testing service would be applied less rigorously to patients who are being treated at other health care facilities. This is not the case. Laboratory physicians routinely collaborate with physicians outside of their health system to provide patient care. The testing service is still developed and optimized for use in a health system’s laboratory or laboratories under the professional expertise and judgment of a physician. That professional expertise and judgment, both by the laboratory physician and the treating physician, are still applied to the patient and his or her sample, even if the patient is not being treated within the laboratory’s health system. This is the reality of modern care, and one mechanism by which patients can access care that best meets their needs. Patients should not be penalized just because a laboratory developed testing service exists outside of the health system in which they are being treated.

Criterion (3), “whether the LDT is comprised of only components and instruments that are legally marketed for clinical use,” would rule out the thousands of laboratory developed testing services that are performed using reagents developed by laboratory physicians as a component part of a laboratory developed testing service, which itself is the practice of medicine. It also rules out the use of instrumentation that is not FDA-approved; very few instruments are FDA-approved, especially those that use newer technologies. This criterion would serve to eliminate almost every laboratory developed testing service from the “traditional LDT” exemption, subjecting them to approval/clearance requirements and almost certainly resulting in laboratories no longer offering the services.

Criterion (4), “whether the LDT is interpreted by qualified laboratory professionals without the use of automated instrumentation or software for interpretation,” again appears to disregard modern laboratory medicine. In today’s technically advanced laboratories, computers and software play a role in nearly every laboratory developed testing service. Key to the use of these computers and software is the oversight of the laboratory physicians and professionals who have developed and optimized their use for the service at hand, and are able to make adjustments when appropriate. Criterion (4) does not acknowledge the professional expertise of the physicians who developed the test and the fact that they will work together with treating physicians to apply results to patient care. It is overly restrictive, and like Criterion (3), would result in many laboratories halting the offering of the service, negatively

impacting patient care. A distinction should be made for commercial kits that use proprietary, complex, and nontransparent algorithms to deliver a result. In this case, neither the laboratory physician nor the treating physician is able to assess the application of such an algorithm to the care of their patients. In contrast to laboratory developed testing services that include algorithms that can be continually assessed and adjusted by the physician and his or her team of laboratory professionals, the AMA believes that commercial kits using these algorithms should undergo premarket review, potentially by the FDA.

The AMA strongly urges the FDA to revise its criteria for a “traditional LDT” and apply enforcement discretion to those laboratory developed testing services that fit the definition proposed above, that is, “a test that is developed, validated and used for planning or implementing patient care, and is intended for use only by the health system in which it was developed.” Health system should include reference laboratories that have an established obligation to provide testing services that are not available within the health system.

Enforcement Discretion for Tests for Rare Diseases

Laboratory developed testing services are often the only option for those with suspected rare diseases. The commercial market for such tests is nearly non-existent, so laboratory-developed tests are a vital tool for patients and their physicians. As currently written, the FDA's proposed exemption for rare disease tests is inadequate in ensuring the continued availability of laboratory developed testing services; the definition pertains to rarely-performed tests, not rare diseases. The very definition of “rare” implies that many people will need to be tested in order to identify one, the equivalent of finding a needle in a haystack. The differential diagnoses for a set of symptoms may call for testing to rule out a rare disease, meaning that far more than only those who are diagnosed with a rare disease will undergo testing. For that reason, the cut-off of 4,000 persons per year being tested (the Humanitarian Device Exemption definition) is unreasonable.

Real Life Implications for Patients

Newborn screening celebrated its 50 year anniversary in 2013. It is a core component of all state public health departments, and is widely considered to be one of the most successful public health programs. Newborn screening is performed on all infants born in a state without regard to social or economic status. One of the primary criteria used to determine whether a condition should be added to newborn screening panels is the risk of death or significant intellectual impairment prior to the presentation of clinical symptoms. Other criteria are disease incidence and the likelihood that a clinician will recognize the disorder in a timely manner. The diagnosis of rare diseases frequently involves an expensive diagnostic odyssey, and often does not occur in time to prevent significant morbidity. Most states screen for the 31 core conditions on the Recommended Uniform Screening Panel promulgated by the Secretary of the Department of Health and Human Services, and many states have expanded their panels to include over 50 conditions. While the majority of the conditions included in screening panels

are considered rare, approximately 1:700 infants have a condition that is detectable by newborn screening.

The U.S.'s newborn screening program is one of the most stunning public health successes in history. The conditions included in testing panels are those which, if not identified within days of birth, can result in serious morbidity and mortality. Many of the conditions being tested are rare diseases, but that does not diminish the public health imperative for them to be identified and diagnosed in patients. Since the number of newborn screening tests that are performed far exceeds the definition of rare disease proposed in the Framework, each one of the dozens of newborn screening tests may be subject to burdensome requirements that could endanger their availability and unravel this public health safety net.

Furthermore, it is our understanding that the 4,000 persons per year limit proposed in the draft guidance refers to the number of people tested across the U.S. in a given year. Since laboratories have no way of knowing how many persons per year have been tested at other laboratories, they would have no idea whether a test they are performing meets or does not meet the rare disease exemption of 4,000 persons tested per year.

We urge the FDA to reconsider the limit of 4,000 persons per year. According to the FDA's Center for Drug Evaluation and Research (CDER) and the 1983 Orphan Drug Act, a rare disease is one that affects less than 200,000 patients in the U.S. The NIH's Office of Rare Diseases Research (ORDR) maintains a list of the nearly 7,000 rare diseases that fall within this definition.² **The AMA believes that continued enforcement discretion should be applied, but not limited, to laboratory developed testing services for diseases that fall under the Orphan Drug Act's and CDER's definition of a rare disease or that are designated by the NIH ORDR as a rare disease. Furthermore, physicians and patients should have standing to file an appeal to add a rare disease that is not otherwise covered where availability and access should be criteria assessed by the Agency when considering whether to grant such an appeal.** Not only does this acknowledge the clinical realities involved in making diagnoses that are often arrived at after ruling out several other possibilities, it removes laboratories from the untenable position of tracking the number of tests other laboratories are performing. Without such reconsideration by the Agency, the risk of patients encountering access problems is high. Because tests for rare diseases often constitute a small volume of testing for most laboratories, premarket review requirements would likely result in laboratories dropping the tests completely, leaving patients and physicians without an option for screening and diagnosis.

Enforcement Discretion & Laboratory Developed Testing Services for Unmet Needs

Many thousands of laboratory developed testing services exist in the absence of commercially-developed kits. The Agency characterizes these as "LDT's for unmet needs" and has proposed continued enforcement discretion for them. These laboratory developed testing services are for a broad range of conditions, and constitute the standard of care. For example, clinical guidelines recommend testing all

² <http://rarediseases.info.nih.gov/gard/browse-by-first-letter>

newly-diagnosed colon cancers for Lynch syndrome, a hereditary colorectal cancer syndrome. Lynch syndrome testing includes assays for mismatch repair variants and microsatellite instability. This type of testing has been available as a laboratory developed testing service for more than 10 years and has been continually improved-upon as new research data emerges (e.g., including BRAF as part of the Lynch syndrome testing protocol). There are no FDA-approved tests for Lynch syndrome. Similarly, commercial kits may be altered for uses that were not included in the indications approved by the FDA. For example, an FDA-approved test kit may only be designed for use on one type of tumor tissue, but laboratory physicians often use their expertise to alter the kit and optimize performance for other types of tissue. Additionally, alterations are routinely made to commercial kits so that they perform optimally under different conditions, like higher or lower altitude, or on different types of instruments. When these alterations are made, the kit becomes a laboratory developed testing service that meets needs not met by the commercial kit.

The nature of infectious disease outbreaks demands that health systems respond rapidly. Laboratory medicine experts are able to fulfill this need by developing tests that accurately identify pathogens far more quickly than would be possible if FDA approval or clearance were required. For example, in April 2009 an unknown respiratory outbreak emerged in the U.S. and Mexico. During the first week of the outbreak, several dozen laboratories had already developed molecular assays that could identify the outbreak as being caused by influenza, and could distinguish the A and B strains. Several of the laboratories were further able to identify the H1N1 virus from other H1 viruses. Most results from these tests were available within 24 hours, speeding treatment of patients and decision-making by public health officials. FDA approval requirements would have severely crippled this response. FDA has the capability to issue Emergency Use Authorization, but these are temporary and therefore do not adequately or permanently address the problem. The public health of this nation depends on these services by laboratories.

Laboratory developed testing services are critical to patient care, and represent rapid, flexible services for patients that cannot be achieved by most commercial test kits. Yet, the FDA's proposed exemption for this category of laboratory developed testing services ends as soon as a commercial kit becomes available. When this happens, every laboratory that has developed a testing service prior to the availability of the kit would need to submit it to the FDA for approval or clearance. The expense and burden required for such an activity would not be feasible for many laboratories, which would then decide not to continue offering the service. This would drive up costs and would freeze further innovation and improvements to the commercial kit, leaving patients without access to cutting-edge care. To subject laboratory developed testing services to these requirements simply because a manufacturer seeks FDA approval of a kit seems to financially reward a manufacturer that was not the first to offer such a test, nor may be offering the superior test. This system will incentivize and reward only those manufacturers with the resources to undertake costly and burdensome premarket review requirements, and will drive laboratory developed testing services out of existence, to the detriment of the patients they serve. Nearly all commercial kits are based on predicate laboratory developed testing services, and yet a manufacturer who can afford to spend the time and money to seek FDA approval is

rewarded for the ingenuity and innovation that resulted from the laboratory developed testing service. This is unfair and contrary to our nation's principles of competition and innovation.

The Agency's proposal to continue enforcement discretion until a commercial kit becomes available seems to undercut its assertion that laboratory developed testing services are risky and dangerous to patients. If this is the case, why propose continued enforcement discretion until a commercial kit becomes available? Why does the laboratory developed testing service suddenly become more risky to patients once a commercial kit is approved? The reality is that the professional expertise of the physician who developed and optimized the testing service, and oversees its appropriate application (and sometimes alterations) for each patient's clinical needs ensures that the service is far safer than the "one-size fits all" application of a kit. The risk associated with a testing service is mitigated by the physician who developed and oversees it, a function that is not wholly present with commercial kits.

The AMA urges the Agency to apply enforcement discretion to all laboratory-developed testing services that fit the definition we have proposed, no matter whether a commercial kit is in existence.

Under a modernized CLIA, this approach ensures safety of the testing service, preserves the practice of medicine, and promotes continued innovation and access.

Risk-Based Oversight

The AMA generally agrees with other major stakeholders that risks posed by clinical tests are different from therapeutic medical devices. **The current FDA medical device classification, therefore, is not appropriate for clinical tests. A new risk-classification for clinical testing, developed with significant stakeholder input, that balances the relative risks posed by clinical tests with the potential benefit of the information they provide would be most appropriate.** As discussed in a previous section, there are distinct differences between physician services and mass produced commercial diagnostic kits shipped all over the nation. In short, manufacturers lose control over the commercial kit once the kit is shipped. In sharp contrast, a physician remains responsible for providing testing services from design to finalizing the report and discussion with the treating physician. Given the risk associated with rapid multiplication of potential erroneous testing that accompanies commercial diagnostic kits, the FDA establishes rigid rules for test performance to substitute for professional judgment that is not appropriate or desirable for physician testing services. In addition, the test results for commercial kits are extremely limited with few details on how the results were produced, which increases risk associated with evaluating implications for a specific patient.

Risk categorization should be determined by (1) the potential of an incorrect test result to cause harm to a patient, and (2) by test characteristics, e.g., test methodology that is not transparent or well-understood (as in the case of tests that use complex algorithms to produce results). The AMA is concerned, however, by the *a priori* classification of some test types as “high risk” in the absence of any formal risk classification criteria by the FDA. The Agency has stated that high-risk tests will be subject to pre-market approval requirements within 12 months of the guidance being finalized, yet guidance laying out risk classification criteria is not planned for release until 2 years after finalization. This leaves physicians and laboratories uncertain of how to determine whether the tests they offer are high-risk and subject to pre-market review within 12 months, and unable to effectively plan for the additional effort and manpower that would be required for pre-market submission. **The AMA urges the Agency to clearly define risk classification criteria before subjecting physicians and the laboratories where they offer their services to burdensome requirements.** Further, we find it puzzling that the FDA has already named certain test classes that will be considered high-risk without stating how risk classification criteria were applied to these tests to place them in the high-risk category. **We believe the Agency should refrain from classifying any laboratory developed testing service until it has released guidance laying out risk classification criteria.**

When taking into account the potential of a misinterpreted result to cause harm to a patient, one must keep in mind a number of “checks and balances” that accompany laboratory developed testing services. Every laboratory performing clinical testing is CLIA-certified, assuring laboratory performance standards and test accuracy and reliability. Additionally, those performing high-complexity tests must undergo regular proficiency testing. Even further, almost every clinical laboratory chooses, and those that perform high-complexity testing are required, to obtain accreditation by a third-party, such as the

College of American Pathologists, which holds laboratories to rigorous quality standards and regular inspections.

Once the laboratory test has been run, it is reviewed and signed by the laboratory director—a physician or laboratory medicine expert who is legally responsible for the result. The ordering physician then receives that result and, often in consultation with the laboratory director, uses his or her expertise to subsequently manage patients. This application of professional expertise—by highly trained experts in laboratory medicine and patient care—is essential in mitigating the risk of harm that could come to a patient through an incorrect result. **This professional responsibility is present now, without FDA oversight of laboratory developed testing services, and will continue irrespective of additional oversight.**

The professional responsibility of a laboratory director is to ensure that a test run in his or her laboratory produces accurate and reliable results. This often means evaluating the methodology and components of tests and optimizing performance in the laboratory. However, it is impossible to apply these activities to many commercial kits that use “black-box” methodology, i.e., those that use complex, non-transparent, or proprietary algorithms to determine a result. Test results that could potentially cause harm to patients if incorrect and do not lend themselves to evaluation by the laboratory physicians and the patient’s treating physician are most concerning to the AMA and are the type of test that belongs in the high-risk category. To the extent that many companion diagnostic tests are run using simple sequencing or variant identification methodology that is transparent and easily evaluated, the AMA believes it is inappropriate for the FDA to assign all companion diagnostic tests to the high-risk category. Aside from the absence of established risk criteria applied to each individual test’s methodology as a basis for their placement in the high-risk category, the FDA appears to be casting aside the risk mitigation that occurs with a physician’s (both ordering and laboratory) oversight and expertise in running the test and subsequently managing the patient. We ask the FDA to consider these points in developing risk classification criteria.

Furthermore, moderate-risk laboratory developed testing services are considered by the FDA to be of a lower risk to the patient than high-risk testing services, but in the draft guidance, it appears that the moderate-risk testing services are subject to a similar degree of reporting as the high-risk test. No explanation for this similar reporting has been provided. Thus, the Agency has, in fact, proposed only two categories of risk.

Additional Comments Related to Risk

FDA should clarify that this Framework does not apply to testing services provided in Phase 1, Phase 2, or other early-phase clinical trials. In addition to excluding diagnostic tests used in early clinical research from the laboratory developed testing services framework, the AMA requests that FDA address whether the framework will apply in addition to or in place of Investigational New Drug (IND) and Investigational Device Exemption (IDE) requirements for laboratory developed testing services used in Phase III clinical studies. Specifically, the AMA suggests that laboratory developed testing subject to IND and/or IDE

requirements should not be viewed as high risk laboratory developed testing services, and should be subject to continued enforcement discretion for both clinical and investigational uses.

Additional Recommendations

Notification

The FDA has proposed imposing both notification and adverse event reporting requirements on low-, moderate-, and high-risk laboratory developed testing services. The AMA strongly urges the FDA to require notification and adverse event reporting for only those testing services where incorrect results could cause harm to patients and the test methodology is not transparent nor well understood (as in the case of tests that use complex and proprietary algorithms to produce results). While there are a number of locations where relevant information on laboratory developed testing services are maintained, the FDA's proposal raises a host of questions about costs and resources to marshal the information for the FDA's consideration and a great deal of ambiguity as to what the FDA would consider a modification in a test or change in the intended use that would trigger a new notification requirement. This is complicated and resource intensive enough as applied to the testing services that will ultimately be categorized by the FDA as high-risk, but this is compounded exponentially as applied to the vast number of testing services and procedures that would be considered low- and moderate-risk tests. The resource costs question has direct implications for patient care as many clinical laboratories have very slim margins and operate at capacity.

To the extent that the FDA utilizes existing sources, funding should be provided by the FDA to aggregate the information from established sources. The AMA supports obtaining this information from the Genetic Test Registry and GeneTests, but notes that this is an extremely limited universe of testing services subject to the reporting requirement. The AMA urges the FDA, as part of a landscape analysis, to more fully vet and obtain information on the existing sources of this information held by third party CLIA accreditors. Ultimately, the most comprehensive source of information would be held or reviewed by CLIA third party accreditors, but information held by CMS should be utilized to the greatest extent practicable to avoid burdensome duplication.

Application of the Unique Device Identifier and Medical Device Tax

The AMA strongly urges the FDA to clarify that laboratory developed testing services are not subject to the unique device identifier (UDI) requirements nor the medical device tax (MDT). Once again, it was clear that when Congress passed legislation establishing the UDI requirements and the MDT, it was not contemplated or intended that physician services and procedures would be subject to these requirements. Laboratory developed testing services are provided within a closed oversight system with extensive oversight and checks and balances to ensure patient safety—they are not devices transported through commerce. The testing services and providers are identifiable to the patient and the treating physician. The cost and practical challenges of establishing a system to assign and track UDIs would be cost prohibitive for laboratories that do not provide volume based care.

Conclusion

The AMA thanks the FDA for its consideration of these comments and recommendations, and stands ready to take part in continued discussions and proposals on the best path forward to ensure that laboratory developed testing services are analytically and clinically valid, remain accessible for patient care, and do not stifle innovation.

Laboratory Testing Services, As The Practice Of Medicine, Cannot Be Regulated As Medical Devices

Paul D. Clement & Laurence H. Tribe

Counsel to the American Clinical Laboratory Association

Paul D. Clement is a partner at Bancroft PLLC. Mr. Clement served as the 43rd Solicitor General of the United States from June 2005 until June 2008. He has argued 75 cases before the United States Supreme Court, including *McConnell v. Federal Election Commission*, *Tennessee v. Lane*, *Rumsfeld v. Padilla*, *Credit Suisse v. Billing*, *United States v. Booker*, *MGM v. Grokster*, *American Broadcasting Company v. Aereo*, and *Hobby Lobby v. Burwell*. Mr. Clement was recognized as the 2012 Lawyer of the Year by The Bar Association of the District of Columbia and was selected by the National Law Journal in 2013 as one of the 100 most influential lawyers in America. He received his bachelor's degree *summa cum laude* from the Georgetown University School of Foreign Service, and a master's degree in economics from Cambridge University. He also graduated *magna cum laude* from Harvard Law School, where he was the Supreme Court editor of the Harvard Law Review. Following graduation, Mr. Clement clerked for Judge Laurence H. Silberman of the U.S. Court of Appeals for the D.C. Circuit and for Associate Justice Antonin Scalia of the U.S. Supreme Court. Mr. Clement is also a Distinguished Lecturer in Law and Distinguished Lecturer in Government at Georgetown University, where he teaches a seminar on the separation of powers.

Laurence H. Tribe is the Carl M. Loeb University Professor and Professor of Constitutional Law at Harvard Law School, where he has taught since 1968 and was voted the best professor by the graduating class of 2000. The title "University Professor" is Harvard's highest academic honor, awarded to just a handful of professors at any given time and to fewer than 75 professors in all of Harvard University's history. Born in China to Russian Jewish parents, Tribe entered Harvard in 1958 at 16; graduated *summa cum laude* in Mathematics (1962) and *magna cum laude* in Law (1966); clerked for the California and U.S. Supreme Courts (1966-68); received tenure at 30; was elected to the American Academy of Arts and Sciences at 38 and to the American Philosophical Society in 2010; helped write the constitutions of South Africa, the Czech Republic, and the Marshall Islands; has received eleven honorary degrees, most recently a degree honoris causa from the Government of Mexico in March 2011 that was never before awarded to an American and an honorary D. Litt. From Columbia University; has prevailed in three-fifths of the many appellate cases he has argued (including 35 in the U.S. Supreme Court); was appointed in 2010 by President Obama and Attorney General Holder to serve as the first Senior Counselor for Access to Justice; and has written 115 books and articles, including, most recently, the widely acclaimed *Uncertain Justice: The Roberts Court and the Constitution* (Holt and Company, 2014) (coauthored with Joshua Matz), selected by the Washington Post as one of the "best non-fiction books published in 2014." Professor Tribe's treatise, *American Constitutional Law*, is the most oft-cited legal text of the last half-century. Former Solicitor General Erwin Griswold wrote that "no book, and no lawyer not on the Court, has ever had a greater influence on the development of American constitutional law," and the Northwestern Law Review opined that no-one else "in American history has simultaneously achieved Tribe's preeminence as a practitioner and scholar of constitutional law."

Executive Summary

Laboratory-developed testing services are an integral and longstanding component of the practice of medicine and have made immeasurable contributions to public health and the treatment of rare and complex diseases. They are developed and performed by thousands of authorized laboratories in the United States to help physicians diagnose diseases and assist them in deciding on a course of treatment.

For decades, laboratory-developed testing services have been comprehensively regulated by both state regulators and the Centers for Medicare and Medicaid Services (“CMS”). CMS administers the detailed requirements Congress enacted in the Clinical Laboratory Improvement Amendments of 1988 (“CLIA”) that were specifically tailored to and targeted at clinical laboratories and their tests.

Nonetheless, despite nearly three decades of comprehensive CMS oversight, the Food and Drug Administration (“FDA”) has recently asserted authority to regulate clinical laboratories and their tests pursuant to the Federal Food, Drug, and Cosmetic Act (“FDCA”). Specifically, FDA has issued “Guidance” documents that assert sweeping authority to treat laboratory-developed testing services as medical “devices” under its jurisdiction and purport to impose all manner of newly-imposed requirements on those services. FDA claims that Congress granted it this expansive and previously unexercised power *nearly 40 years ago*, through provisions that (unlike CLIA) do not even *mention* laboratories or laboratory testing services and expressly disclaim any intent to regulate the practice of medicine.

FDA’s novel effort to expand its jurisdiction is foreclosed by the plain text of the FDCA. Congress gave FDA the authority to regulate medical devices, and laboratory-developed testing services are not devices. Moreover, FDA’s effort to expand its jurisdiction will directly interfere with the practice of medicine, and will disrupt the ability of doctors to obtain the laboratory tests they need to provide the best possible care to their patients.

Recognizing the futility of asking Congress to grant it the unprecedented authority it now seeks to assert, FDA has proceeded on its own. But, whatever the rationale for its current approach, it is a dramatic overreach. FDA is attempting to saddle a dynamic and innovative industry with sweeping new regulatory burdens without any statutory basis. Worse still, FDA’s attempt to address laboratory-developed testing services as though they were medical devices is an impermissible effort to force a square peg into a round hole. The proper regulatory regime for manufactured articles of commerce—like drugs and medical devices—is simply not a suitable approach for laboratories that provide a service to individual physicians as part and parcel of the practice of medicine. To the contrary, laboratory testing services and medical devices raise completely different regulatory issues—as Congress itself recognized in enacting a distinct regulatory framework for clinical laboratory tests in CLIA, and in charging CMS rather than FDA with CLIA’s oversight of laboratories.

FDA’s attempt to impose burdensome requirements on laboratory-developed testing services through its Guidance documents is unlawful for a second reason as well: the effort violates bedrock principles of administrative law. In its haste to broaden its regulatory reach, FDA has bypassed the notice-and-comment procedures that are a prerequisite to the kind of binding rules that it seeks to impose on clinical laboratories. The agency’s use of Guidance documents in this setting is not some technical “foot fault.” It improperly circumvents the carefully crafted requirements of the Administrative Procedure Act—no mere bureaucratic enactment but a cornerstone, ever since 1946, of the administrative state. Courts and Congress alike have treated

broad delegations of power to executive agencies as permissible over the past six decades only because those agencies are duty-bound to comply with the APA. But FDA use of a Guidance document to effect substantive regulatory change lawlessly shields the agency from the congressional mandate that it meaningfully consider and respond to the comments it receives in the course of the public procedures Congress required. By proceeding via a Guidance approach, FDA is also impermissibly seeking to avoid assessing the enormous economic impact of its proposal and to avoid determining whether the benefits it would supposedly provide justify the costs it would undoubtedly impose. That is why the American Medical Association, American Hospital Association, and many leading medical providers have all requested that FDA withdraw its misguided Guidance proposal.

For all these reasons, FDA should withdraw its proposed Guidance.

Analysis

I. LABORATORY-DEVELOPED TESTING SERVICES ARE MEDICAL SERVICES

Laboratory-developed testing services are “in house” diagnostic tests developed, validated, and performed by highly trained professionals within a single clinical laboratory. Quite simply, physicians routinely depend on laboratory-developed tests in making crucial medical decisions for their patients. They are part and parcel of the practice of medicine. Therefore, it is not surprising that the American Medical Association and many leading medical providers have asked FDA to withdraw its proposed regulatory framework.

Laboratory-developed testing services are performed on blood, urine, tissue or other types of specimens at the request of an individual doctor, in the context of a specific doctor-patient relationship. Like the individual doctors themselves, the laboratories offer no physical product, but rather provide clinical information to physicians and their patients. A laboratory-developed testing service is a methodology or process—based on a laboratory’s unique knowledge of the protocols, performance characteristics, and means of analysis—by which the laboratory generates biochemical, genetic, molecular, or other forms of clinical information about a patient specimen that is provided to the treating physician.

Unlike a drug or device, which is a finished, packaged, off-the-shelf article of commerce accompanied by instructions for use by others, a laboratory-developed testing service is a proprietary methodology that is performed only by the developing laboratory. That service in turn generates a report of test results—for instance, whether the patient’s specimen contains a particular biomarker or analyte—that the laboratory transmits to the ordering physician. The testing service is not sold as a kit, and the protocol is not transferred in any manner to other laboratories, hospitals, or other facilities outside the developing laboratory entity; indeed, it is not distributed commercially at all. No physical product is sold. No article of personal property is transferred such that title passes from one party to another.

As FDA itself has recognized, such testing services are widely employed by doctors in their “clinical decision making and disease management, particularly in the context of personalized medicine.” FDA, Oversight of Laboratory Developed Tests, 75 Fed. Reg. 34,463 (June 17, 2010); *see also id.* (“they are often used ... *to inform* critical treatment decisions”) (emphasis added). In a hypothetical world of unlimited resources, doctors with access to cutting-edge scientific knowledge and equipment might in theory perform these tests in their own clinics, much like general practitioners might in theory perform specialized cardiac or neurological procedures in their own clinics. However, as with other medical specialties, referring these tests to professional laboratories is vastly more realistic and efficient and provides doctors and patients with access to a far larger and more up-to-date universe of potentially life-saving tests. Once a doctor receives the clinical information generated at that doctor’s request by the laboratory, the doctor reviews the results and makes his or her own diagnosis and treatment recommendations for the patient based on all the clinical information the doctor has obtained. Thus, unlike drugs or devices—which again are articles of commerce that are intended to be employed in the same way by any user, based on the manufacturer’s instructions—laboratory-developed testing services are developed by a laboratory for use only by that specific laboratory.

Doctors routinely rely on laboratory-developed testing services ranging from routine tests such as pap smears and gram stains, to the most advanced and sophisticated molecular and genetic sequencing tests for cancer, heart disease, and rare and infectious diseases. *See, e.g., Association for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107 (2013) (patent case addressing

laboratory-developed testing service for breast cancer risk by Myriad Genetics). While there are numerous, ready-made *in vitro* diagnostic test kits available in the marketplace, those commercially distributed kits address only a miniscule fraction of the situations in which laboratories can provide doctors with valuable diagnostic information. And even in situations in which commercially distributed test kits are available, the kits are frequently inadequate for patients who have particularized needs. For example, the FDA-approved BRAF test kit, used to characterize metastatic melanoma and other cancers, can detect mutated forms of the BRAF gene, but is unable to distinguish between two different mutational variants (V600E and V600K), each of which indicates very different treatments. Furthermore, for patients of Asian and Italian descent, there are additional genetic markers (*e.g.*, CKIT), not included in the FDA-approved test kit, which should be tested for in order to fully inform treatment decisions. Laboratory-developed tests have been formulated to meet these otherwise unmet clinical needs and provide physicians with the vital information they need to best treat their patients. In many instances, test kits are already outdated by the latest scientific knowledge upon their approval by FDA, and there are many biomarkers and analytes for which no standardized test kit yet exists. Where test kits would not generate the economies of scale necessary to justify a commercially marketed product—as with many rare diseases or conditions—laboratory-developed testing services are often the only available option. Such testing services include:

- “Gold standard” DNA sequencing and RNA expression tests, including those for Gaucher disease, Canavan disease, Niemann Pick disease, multiple endocrine neoplasia, hereditary nonpolyposis colon cancer (HNPCC), breast cancer, and hereditary deafness;
- Karyotype/chromosome/cytogenetic tests, such as those used to detect leukemia, lymphoma, developmental delays, and mental retardation;
- Newborn screening tests for metabolic disorders;
- Tests for rare diseases, including many tests used in Ashkenazi Jewish screening (*e.g.*, tests for Tay-Sachs disease) and tests for herpes simplex encephalitis, muscular dystrophies, hereditary hemochromatosis, Prader-Willi/Angelman syndromes, neurofibromatosis (types 1 and 2), and congenital adrenal hyperplasia; and
- Child evaluation tests for developmental delays, such as Fragile X Syndrome testing and chromosome analysis.

History shows that tests are most often created in response to an otherwise unmet clinical need, or where the existing diagnostic tests are insufficient or fail to incorporate the most recent breakthroughs in scientific and medical research. Laboratories developed specialized tests for various cancer biomarkers, including KRAS (an oncogene frequently associated with colorectal, lung, pancreatic and other cancers), several years before FDA-approved test kits reached the general market. Laboratories likewise developed tests for emerging infectious diseases, such as HIV, SARS and H1N1, long before FDA-approved tests were available. In addition, laboratories validated a Western blot test to diagnose HIV-1 two years before an FDA-approved Western blot test became commercially available. Laboratory-developed testing services routinely represent the gold standard in facilitating the highest quality medical care.

In providing these medical services, laboratories are subject to comprehensive regulation by CMS, by state regulators, and often by “deemed authorities” under the CLIA program, including the Joint Commission on Oversight and the College of American Pathologists. These “deemed authorities” perform their own rigorous inspections to ensure that CLIA standards are

met and in some instances go even beyond those requirements. Laboratories regulated under CLIA are all required to be CMS-certified and state-certified as well. Those certifications ensure that the laboratories provide accurate information to doctors and that their testing processes are supervised by qualified personnel. For example, CLIA requires a qualified medical director to oversee all high-complexity clinical tests, and subjects each laboratory-developed test to analytical validity regulations to ensure that it does in fact accurately identify or measure the analyte (*e.g.*, genotype, chemical, protein) that it purports to identify or measure. Nonetheless, precisely because the tests need *not* undergo the time-consuming premarket FDA approval process required of drugs and devices, laboratories are able to continually and rapidly innovate and improve their services. Laboratories have the flexibility and technical expertise to adapt in real time to the latest scientific advances. Laboratories continually modify and validate their tests to ensure that they reflect the most up-to-date technological know-how, scientific breakthroughs, and published research that will enable doctors to better serve their patients when the need arises, not when it is too late to be of use.

II. FDA’S SWEEPING ASSERTION OF JURISDICTION OVER LABORATORY-DEVELOPED TESTING SERVICES FLOUTS THE DECISIONS MADE BY CONGRESS

Both the text of the FDCA and the broader statutory context clearly foreclose FDA’s attempt to expand its jurisdiction to cover laboratory-developed testing services. Congress has expressly considered the unique regulatory issues raised by clinical laboratories and the tests they develop and perform. But it expressly addressed those issues through the comprehensive and entirely distinct statutory regime of CLIA, *not* through the FDCA. And Congress vested authority over those regulations in CMS, *not* in FDA. The text of the FDCA reflects this basic division of labor by granting FDA authority over “devices,” defined in terms that make clear that devices are articles of commerce, not the kinds of services performed by doctors and laboratories. Congress reinforced this division of labor by expressly precluding FDA from interfering with the practice of medicine. Moreover, multiple canons of construction, including the presumption against grants of controversial but long dormant regulatory authority and the rule of lenity, underscore that Congress did not *sub silentio* grant FDA the enormous regulatory power it seeks to exercise. FDA’s attempted expansion of its authority is flatly inconsistent with the statutory text, would transgress the explicit limitation against interfering with the doctor-patient relationship, and would raise serious constitutional questions that Congress itself sought to avoid.

A. FDA Has Asserted Sweeping Authority Over Laboratory-Developed Tests

Although laboratory-developed testing services have long been regulated both by the states and by CMS, FDA recently announced its own sweeping efforts to regulate those services via “Guidance” documents that purport to impose all manner of requirements through an elaborate, nine-year phased-in timetable. FDA’s assertion of regulatory authority is premised on the rather remarkable claim that the 1976 Medical Device Amendments (“MDA”) to the FDCA—enacted nearly four decades ago—rendered *all* laboratory-developed testing services “unapproved devices” under its jurisdiction. FDA posits that Congress took that dramatic step in provisions that did not mention laboratories, laboratory tests, or laboratory testing services, in a statute that specifically excludes from FDA’s jurisdiction any power to regulate the practice of medicine, and that is focused on the distinct problems concerning manufactured, mass-marketed, and widely-distributed drugs and devices moving in interstate commerce.¹

¹ The record shows that, in fact, the first time that FDA made a public claim about its supposed authority to regulate laboratory-developed testing services as devices was in a draft

The requirements FDA seeks to impose under its newly asserted authority are substantial. FDA’s so-called Guidance documents seek to impose significant, binding requirements on private parties that provide laboratory-developed testing services. In seeming recognition that FDA lacks the resources to regulate the entire range of laboratory-developed testing services over which it belatedly claims jurisdiction, the Guidance announces a risk-based, phased-in approach to a “Framework for Regulatory Oversight of Laboratory Developed Tests.” The main elements of this new Framework include numerous obligations that laboratories must observe in order to comport with numerous medical device regulations. These obligations include:

- Giving notification to FDA about, or registering and listing of, laboratory-developed testing services (and “significantly” changed laboratory-developed testing services) under 21 C.F.R. Part 807, to assist FDA in determining their risk classification and what premarket review requirements to enforce against which tests;
- Reporting of “adverse events” involving laboratory-developed testing services under 21 C.F.R. §803.50, whenever a laboratory that develops in-house tests or significantly modifies FDA-approved test kits becomes aware of any information that reasonably suggests that their test may have caused or contributed to death or serious injury;
- Submitting for premarket review “high-risk” and “moderate-risk” laboratory-developed testing services to assess their clinical validity, *see* 21 C.F.R. Part 814;
- Complying with Quality System Regulations, including the device-related design control procedures of 21 C.F.R. §820.30(a)-(j); and
- Demonstrating the “clinical validity” of laboratory-developed testing services.

These requirements are not uniformly imposed on all laboratory-developed testing services. Instead, FDA would classify laboratory testing services and, based on that classification, FDA would phase in requirements over a nine-year period after the Guidance is finalized. The Guidance documents thus envision that the contemplated regulatory regime will not be fully in place until 2024, at the earliest.

B. FDA’s Interpretation Is Foreclosed By The FDCA’s Plain Text

FDA’s assertion of authority over laboratory-developed testing services is clearly foreclosed by FDA’s own authorizing statute, the FDCA. On the face of the statute, laboratory-developed tests fall outside the ambit of FDA’s authority for at least three reasons: (1) they are not “devices” under 21 U.S.C. §321(h); (2) they are not “introduc[ed] into interstate commerce for commercial distribution” under 21 U.S.C. §360(k); and (3) they directly implicate the practice of medicine exempted under 21 U.S.C. §396.

1. Laboratory Testing Services Are Plainly Not “Devices”

Compliance Policy Guide in 1992. After objections, FDA removed any reference to laboratory tests in the final Compliance Policy Guide, released in 1996. It was not until 1996 that FDA announced in the Federal Register that it believed it had authority to regulate laboratory-developed testing services but was not exercising that power as a matter of discretion. Clinical laboratories and others filed comments challenging FDA’s assertion that it had the authority to oversee such testing services for twenty years but simply never used that authority. In any event, the legal analysis in this memorandum would not be affected even if FDA had consistently asserted the authority to regulate laboratory-developed tested services.

With the FDCA, Congress authorized FDA to protect the public health by regulating the safety and effectiveness of “any food, drug, device, tobacco product, or cosmetic” that is “introduc[ed] into interstate commerce.” 21 U.S.C. §331(a). Under the FDCA, therefore, FDA has authority to regulate manufacturers only of commercially distributed medical “devices,” including devices used to perform standardized clinical tests (so-called “test kits”). But laboratory-developed testing services are *processes* and *methodologies* that are qualitatively and categorically different from the tangible goods that FDA may regulate as “devices.” Statutory text, basic principles of interpretation, and common sense leave no doubt that laboratory-developed testing services are not medical “devices” under the FDCA.

In common usage, a “device” is a *physical article or product*. See *Oxford Dictionary of English* (3d ed.) (2010) (defining “device” as “a thing made or adapted for a particular purpose, especially a piece of mechanical or electronic equipment”); *American Heritage Dictionary* (5th ed. 2014) (defining “device” as “[a]n object designed and manufactured to perform one or more functions”). Laboratory-developed testing services are self-evidently not “devices.” Such in-house tests are proprietary *methodologies* rather than physical *products*. That is, laboratories provide a purely informational service, using their unique knowledge of the protocols, the performance characteristics, and the means of analyzing each test, to generate clinical information about a specimen for the ultimate use of the treating physician.

Consistent with the plain, common-sense meaning of “device,” the FDCA defines that term as “an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory,” that satisfies various specified criteria.² 21 U.S.C. §321(h). The words grouped in §321(h) are, without exception, *physical articles* that move in interstate commerce. “The traditional canon of construction, *noscitur a sociis*, dictates that words grouped in a list should be given related meaning.” *Dole v. United Steelworkers of Am.*, 494 U.S. 26, 36 (1990) (“*noscitur a sociis*” literally means “it is known by the company it keeps”). Here, the statutory text itself reflects and reinforces that traditional canon by employing an inclusive catch-all term that uses the word “article.” In-house laboratory testing services are not physical “articles,” much less articles moving in commerce, and are categorically different from the items Congress enumerated as “devices.” Sweeping proprietary *methodologies* and *processes* into a list that includes only tangible articles would contravene the basic rule of construction that “words ... are known by their companions.” *Gutierrez v. Ada*, 528 U.S. 250, 255 (2000).

FDA asserts that Congress’ addition of “in vitro reagents” to §321(h) in the 1976 MDA was intended to sweep in all laboratory-developed testing services. But a testing service is not a “reagent.” Reagents are chemical substances or mixtures, *i.e.*, physical articles, that are separate and distinct from services that make use of them as part of their procedures. Indeed, the inclusion of reagents as an additional statutory example of a “device” cuts *against* FDA’s interpretation because it confirms that Congress focused its device definition on *physical articles*. See H.R. Rep. No. 94-853, at 14 (1976) (new definition “retain[ed] (in somewhat more precise detail) provisions

² A “device” must be: (1) “recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,” “intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals,” *or* “intended to affect the structure or any function of the body of man or other animals,” *and* (2) “not achieve its primary intended purposes through chemical action within or on the body of man or other animals and ... not [be] dependent upon being metabolized for the achievement of its primary intended purposes.” 21 U.S.C. §321(h).

of existing law that a device is *an article or component thereof*) (emphasis added). Had Congress wished to defy the ordinary conventions of the English language and define a “device” as “any process that *uses* a reagent,” it could easily have done so. It did not, and nothing in the Act suggests that Congress subjected clinical laboratory methodologies to the FDCA’s “device” regulations.

When the statutory text is this clear, there is no need for resort to legislative history. *See Ratzlaf v. United States*, 510 U.S. 135, 148 (1994). But here, the legislative history underscores that Congress used “device” in its ordinary sense and that the 1976 MDA did not introduce any sweeping change in the statute’s device coverage. To the contrary, the House Reports repeatedly referred to “devices” as “products” and “articles.” *See* H.R. Rep. No. 94-1090, at 62, 65 (1976) (Conf. Rep.); H.R. Rep. No. 94-853, at 6 (1976).

It is far-fetched to suppose that laboratory-developed testing services *become* medical devices in their own right merely because they sometimes *utilize* other medical devices. FDA’s own regulations recognize the distinction between a service that uses devices and a device itself. For example, the FDA regulation excluding laboratories from device registration requirements specifically recognizes that laboratories’ “primary responsibility to the ultimate consumer is to ... provide a service *through the use* of a previously manufactured device.” 21 C.F.R. §807.65(i) (emphasis added). Laboratories may well draw on both reagents and laboratory equipment of many kinds in executing their clinical testing services, but that plainly does not render the services these laboratories perform *themselves* “medical devices.” A contrary view would mean that all surgical procedures and physical examinations that may *use* devices—*i.e.*, virtually *every* medical procedure (except perhaps those few procedures that use only a physician’s own eyes, ears, and hands)—would be deemed “devices” subject to the FDCA’s regulations. For example, every time a radiologist reads an x-ray, he or she is providing a service that depends on a medical device—the x-ray machine. However, the radiologist is rendering a service, and is not subject to regulation under the FDCA. It is plainly not the law that a surgical procedure like an appendectomy is itself a “device” merely because it *uses* devices such as surgical instruments, sutures, and other medical equipment. *Cf. Nixon v. Mo. Mun. League*, 541 U.S. 125, 138 (2004) (courts should not construe statutes to produce absurd results).

Nor does it matter that a particular laboratory-developed testing service may be *functionally similar* to some kind of device. FDA heavily emphasizes, for example, that *in vitro* diagnostic (“IVD”) test kits perform clinical testing functions that are *similar* to laboratory-developed testing services. *See* FDA Denial of ACLA Citizen Petition (“FDA Denial”) at 4-5. But IVD test kits are devices by any plausible reading of the statutory definition; laboratory testing services do not become “devices” because they allow physicians to accomplish similar ends. FDA ignores the fact that the statute does not classify based on functionality, but on whether something is a physical article that a manufacturer commercially distributes in interstate commerce. Not only does a functional approach have no basis in the statutory text, but it would be completely unworkable in practice. Most medical devices are designed to allow a treating physician to perform some function more effectively, and many are substitutes for a service that the doctor would otherwise perform. For example, a sophisticated medical device may obviate the need for a more invasive or riskier form of surgery, but the functional similarity of a doctor’s service to a medical device does not thereby turn the doctor’s service into a device.

Once again, the legislative history confirms what the text makes clear. Congress had IVD *products* in mind (unlike in-house laboratory testing *services*) in enacting the MDA amendments to the “device” definition. The Senate Report specifically noted that the “in-vitro diagnostic *products*” covered by the new definition “include those *products* which are not ingested and which are used to assist in the diagnosis of disease or other conditions of the body.” S. Rep. No. 94-33,

at 17 (1975) (emphases added). Where the statute itself draws a distinction between devices and non-devices, FDA may not conjure up regulatory gaps based on functional resemblances and then use that purported similarity to expand its own jurisdiction.³

At bottom, plain text, basic principles of statutory interpretation, and common sense foreclose FDA's assertion of authority over laboratory-developed testing services. FDA jurisdiction over those services would require not merely a "broad" reading of section 321(h), but a rewriting of the statute.⁴

2. Laboratory-Developed Testing Services Are Not Introduced Into Interstate Commerce for Commercial Distribution

Section 510(k) of the FDCA, which applies FDA's approval and clearance requirements only to devices that *both* move in interstate commerce *and* are commercially distributed, further underscores that Congress did not remotely mean to grant FDA authority to regulate laboratory-developed testing services. Section 510(k) provides:

Each person who is required to register under this section and who proposes to begin the introduction or delivery for introduction into interstate commerce *for commercial distribution* of a device intended for human use shall, at least ninety days before making such introduction or delivery, report to the Secretary . . . action taken by such person to comply with requirements under section 360d [related to performance standards] or 360e [related to premarket approval] which are applicable to the device.

21 U.S.C. §360(k). FDA has defined "commercial distribution" to mean "any distribution of a device intended for human use which is held or offered for sale," 21 C.F.R. §807.3(b), and to generally require delivery to purchasers or consignees. FDA Manual of Compliance Policy Guides §300.600 (1978, reissued 1987) ("CPG").

Laboratory-developed testing services obviously do not move in interstate commerce. Indeed, FDA itself acknowledged this fact in the preamble to its rule governing analyte specific reagents ("ASRs"), stating that the focus of its rule was "the classification and regulation of ASR's *that move in commerce*, not tests developed in-house by clinical laboratories." Medical Devices; Classification/Reclassification; Restricted Devices; Analyte Specific Reagents, 62 Fed. Reg. 62,243, 62,249 (Nov. 21, 1997) (emphasis added). Unlike IVD test kits, which are mass-produced, mass-distributed products delivered to numerous laboratories and consumers, the laboratory-developed testing services are not commercially distributed. The testing services are performed in-house and the proprietary methodologies employed in the in-house testing are specific to the individual laboratory entity and never leave its confines. And while the results of the testing services do leave the laboratory, they are not commercially distributed, but rather are communicated to the requesting physician and patient. None of this is to suggest that Congress could not regulate the laboratories and their testing services as a valid exercise of its commerce power. Indeed, Congress has done just that in other statutes. But the Medical Device

³ FDA regulations that define "devices as defined in section [321](h)" as including several "[i]n vitro diagnostic *products*" only confirm that the "device" definition covers products, not services. 21 C.F.R. §809.3(a) (emphasis added).

⁴ Even the sole district court case that FDA cites as supporting a "broad" understanding of "device" involved a physical instrument, and does not sweep nearly as broadly as FDA's current theory. See *United States v. 22 Rectangular Or Cylindrical Finished Devices*, 714 F. Supp. 1159, 1165 (D. Utah 1989) (upholding FDA's determination that a sterilizing *instrument* that did not come into direct contact with patients was a "device").

Amendments of 1976 were, as their name suggests, directed at devices, which Congress understood to be physical articles that can be introduced into commerce and commercially distributed. The fact that laboratory-developed testing services are not commercially distributed is just one more indication that Congress did not intend to reach those services in the MDA.

FDA argues that the “commercial distribution” requirement is satisfied here because laboratory-developed tests “are *offered* commercially for use in the diagnosis/treatment of patients,” such as through “promot[ion] . . . on their website.” FDA Denial at 13 (emphasis added). Mere promotion, however, is not sufficient to establish commercial distribution. Nobody would describe an interstate advertisement as the “commercial distribution” of either the words comprising the advertisement or of the goods or services the advertisement describes and promotes. The legislative history of the MDA confirms this commonsense conclusion by specifically noting that “commercial distribution” does *not* include “mere announcements of intent to market a device.” H.R. Rep. 94-853, at 36 (1976). Even FDA’s own Compliance Policy Guide, moreover, has clarified that offering a device for sale is not enough; a manufacturer must show that (1) it advertised, displayed, or offered the device for sale, (2) the device was not offered or accepted only for research or investigational use, *and* (3) the manufacturer had accepted or was prepared to accept a purchase order, generally with delivery to follow. CPG §300.600. Indeed, far from being commercially distributed, laboratory-developed testing services are often required precisely because the same clinical information *cannot* be obtained from commercially distributed test kits. And, of course, the promotion of a service is very different from the distribution of an article—as different, indeed, as the provision or advertisement of medical advice is from the sale of a stethoscope or a syringe.

In short, the statute’s commercial distribution requirement underscores the FDCA’s focus on problems arising in connection with manufactured, mass-marketed, and widely-distributed drugs and devices—yet another indication of Congress’ intent to regulate products far afield from the informational in-house services of laboratories to meet the needs of individual patients.

3. Regulating Laboratory Testing Services As Devices Would Interfere With The Practice Of Medicine

That laboratory-developed testing services fall outside of the FDCA’s device definition is further confirmed by Congress longstanding reluctance to interfere with the practice of medicine, which is underscored by an express statutory disclaimer of such interference. Congress enacted the FDCA and its “device” definition in 1938 against a well-established background understanding that “direct control of medical practice in the states is beyond the power of the federal government.” *Linder v. United States*, 268 U.S. 5, 18 (1925); *see also Rush Prudential HMO, Inc. v. Moran*, 536 U.S. 355, 387 (2002) (establishing “standards of reasonable medical care” is a “quintessential[] state-law” function). As the Act’s sponsor, Senator Royal Copeland, explained, “the bill is not intended as a medical practices act and will not interfere with the practice of the healing art by [persons] in the States where they are licensed by law to engage in such practice.” S. Rep. No. 74-361, at 3 (1935). In fact, a bill seeking to clarify that the definition of “drug” did not encompass any “medicine prepared and dispensed by a physician in the course of his professional practice” was rejected as superfluous because there was “nothing in the [FDCA] which would interfere at all with the ordinary legal practice of medicine.” Peter Barton Hutt, *Regulation of the Practice of Medicine Under the Pure Food and Drug Laws*, 33 Q. Bull. Ass’n of Food & Drug Off. 1, 8 (1969).

In 1997, Congress added a provision making *explicit* what had always been implicit: that the FDCA does not regulate the practice of medicine. Section 1006 provides: “Nothing in this chapter shall be construed to limit or interfere with the authority of a health care practitioner to

prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship.” 21 U.S.C. §396. That provision, as the Supreme Court has recognized, reinforces that FDA’s “mission [is] to regulate ... without directly interfering with the practice of medicine.” *Buckman Co. v. Plaintiffs’ Legal Comm.*, 531 U.S. 341, 350 (2001). “FDA is charged with the difficult task of regulating the marketing and distribution of medical devices without intruding upon decisions statutorily committed to the discretion of health care professionals.” *Id.*

However, laboratory-developed testing services are part and parcel of the practice of medicine. To regulate the generation of information that a physician asks a consultant or a consulting laboratory to provide—by performing tests on specimens provided by the physician in order to assist that physician in diagnosing the patient’s illness or in prescribing a course of treatment—interferes with that physician’s decisions of what to prescribe or administer to his or her patient. In fact, in a hypothetical world of unlimited resources, highly-trained doctors with access to cutting-edge scientific knowledge and equipment might in theory perform these tests in their own clinics, much in the same way that a general practitioner in a hypothetical world of unlimited resources might in theory be able to perform specialized cardiac or neurological procedures in their own clinics. However, as with other medical specialties, referring these tests to professional laboratories is far more realistic and efficient and provides doctors and patients with access to a far larger and more up-to-date universe of potentially life-saving tests.

For instance, clinical laboratories routinely perform tests that are premised on new scientific developments, are used to test for unique or complicated conditions, or are more sensitive and sophisticated than off-the-shelf FDA-approved test kits. That referral of responsibility, however, does not change the fact that the tests are merely an extension of the *doctor’s* favored methods for evaluating a patient and diagnosing the problem. Whether outsourced or not, the testing methodology is part and parcel of the doctor’s practice of medicine, not materially different from the same doctor’s consultation of an up-to-date, peer-reviewed medical journal or clinical examination of their own patient. The laboratory offers the doctor an objective array of factual information—for instance, a patient’s genetic predisposition to a particular disease—from which the doctor draws his or her *own* interpretation, diagnosis, and treatment recommendations.

In this respect, laboratory-developed testing services are fundamentally different from drugs and devices—products that *themselves* promise to yield a particular diagnosis or treatment upon application to the patient and that are accompanied by instructions for use. Laboratory-developed testing services, by contrast, are developed and performed at the request of an individual doctor, within the context of a doctor-patient relationship, to inform the doctor’s independent diagnosis and treatment decisions. The laboratories provide no physical product. They provide a *medical service*, just as physicians do.

Regulating laboratory-developed testing services as devices, as FDA seeks to do, would thus fundamentally “interfere with the authority of ... health care practitioner[s]” to make diagnosis and treatment decisions. 21 U.S.C. §396.

Remarkably, FDA does not dispute that its actions will interfere with the diagnosis and treatment decisions of doctors. Instead, FDA contends that section 1006 only protects doctors’ right to administer “legally marketed” devices, not “unapproved” devices. But FDA’s contention is hopelessly circular: the question to be answered here is whether laboratory-developed testing services are “devices” subject to approval by FDA, and the fact that treating them as such would interfere with the practice of medicine is itself an important reason for concluding that they are not. Similarly, the mere possibility that a laboratory-developed testing service could potentially *use* an “unapproved” device—such as an unauthorized reagent, over which FDA *does* have

jurisdiction—does not and cannot bring the *services themselves* within FDA’s regulatory reach. Just as a doctor’s use of an unapproved device in treating a patient would not render the doctor’s medical services “devices” under the FDCA, so too a laboratory’s hypothetical use of an unapproved reagent in conducting a testing service would not suddenly transform its testing service into a “device”—particularly because, in both cases, the assertion of FDA authority would be a brazen interference with the practice of medicine.

In all events, FDA’s premise—that doctors, in relying on laboratories and their testing processes in their practice of medicine, are using “unapproved” devices—only underscores the extreme implications of FDA’s broad interpretation of the FDCA: that the entire medical profession has, unbeknownst to doctors, been involved in the widespread illegal distribution of unapproved medical devices since 1976. Under FDA’s theory, every doctor who sends a specimen for analysis via a laboratory-developed testing service is really soliciting an unlawful medical device. *See* 21 U.S.C. 331(c) (prohibiting receipt of a misbranded medical device). Moreover, FDA’s theory necessarily means that an entire laboratory-testing industry has been unwittingly operating in violation of a number of criminal statutes for decades, spared from prosecution only by FDA’s grace. As the Seventh Circuit concluded in rejecting a similarly sweeping government theory in a different context, the far “more plausible hypothesis” is that the industry’s practice is simply not unlawful. *Yi v. Sterling Collision Centers, Inc.*, 480 F.3d 505, 510-511 (7th Cir. 2007).

In sum, the FDCA’s practice-of-medicine exception is further evidence that Congress did not intend to treat in-house tests developed by laboratories as “devices.” Both doctors and patients would ultimately suffer the adverse consequences of subjecting laboratory-developed tests to FDA’s clearance and approval requirements. Because obtaining FDA pre-approval is often not financially feasible for tests that serve only small patient populations, and because obtaining FDA re-approval is not workable for laboratories that continually modify thousands of in-house tests, the end result would be less laboratory-generated clinical information that doctors can use to assess and care for their patients. Nothing in the FDCA remotely contemplates, let alone compels, this harmful and potentially life-threatening interference with the practice of medicine.

C. Bedrock Principles of Statutory Construction Reinforce The Conclusion That FDA Lacks Jurisdiction

Two bedrock principles of statutory interpretation further reinforce the conclusion that FDA lacks the sweeping authority over laboratory-developed testing services it now belatedly asserts.

First, Congress is presumed not to address issues of great “economic and political significance” in a “cryptic ... fashion.” *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 160 (2000). Congress “does not, one might say, hide elephants in mouseholes.” *Whitman v. Am. Trucking Ass’ns*, 531 U.S. 457, 468 (2001). For decades, countless clinical laboratories have openly developed in-house tests—up to thousands of in-house tests per laboratory—without seeking premarket approvals from FDA, and have also modified FDA-approved test kits without reapplying for new approvals. Innumerable doctors have widely employed such laboratory-developed testing services to obtain clinical information to help them diagnose and treat their patients. It is late in the day indeed to conclude that all these laboratories and physicians have been unlawfully utilizing unregistered medical devices for all these years based on a statutory provision no one understood to have this dramatic effect. It is little wonder then that the American Medical Association, together with American Hospital Association, Coalition for 21st Century Medicine, Emory University, LabCorp, Mayo Clinic, Miraca Life Sciences, Quest Diagnostics and Seattle Children’s Hospital, have separately expressed grave concern about FDA’s proposal.

FDA’s position—that Congress in 1976 *sub silentio* subjected in-house laboratory tests to FDA premarket clearance and approval requirements—would have a breathtaking economic impact on traditional laboratory practices, on the physicians who rely on laboratory medicine to facilitate their diagnostic and treatment decisions, and on the allocation of regulatory authority between FDA and CMS. “When an agency claims to discover in a long-extant statute an unheralded power to regulate ‘a significant portion of the American economy,’ we typically greet its announcement with a measure of skepticism.” *Util. Air Regulatory Grp. v. E.P.A.*, 134 S. Ct. 2427, 2444 (2014). Congress is presumed not to have dramatically upended a well-settled regulatory landscape without some clear indication in the relevant statutory text and history. *See id.*; *Brown & Williamson*, 529 U.S. at 160). FDA’s assertion of an “unheralded authority” to regulate thousands of laboratories already subject to regulation by CMS and state regulators “falls comfortably within the class of authorizations that we have been reluctant to read into” statute in the absence of unambiguous text. *Util. Air Regulatory Grp.*, 134 S. Ct. at 2444.

Second, the “rule of lenity” requires that when a statute carries criminal penalties, “less constrained” constructions must be rejected absent “Congress’ clear instruction otherwise.” *Skilling v. United States*, 561 U.S. 358, 411 (2010). Basic principles of due process require that a federal statute define the conduct it proscribes with specificity so that ordinary persons are on notice of what conduct is prohibited and required. *United States v. Lanier*, 520 U.S. 259, 266 (1997).

That tenet squarely applies to the FDCA, which provides for both civil *and criminal* penalties for violations, *see* 21 U.S.C. §331, 333(a), and must be interpreted consistently in both contexts. *See Clark v. Martinez*, 543 U.S. 371, 380 (2005); *Leocal v. Ashcroft*, 543 U.S. 1, 11-12 n.8 (2004). Moreover, “where, as here, an agency’s announcement of its interpretation is preceded by a very lengthy period of conspicuous inaction, the potential for unfair surprise is acute.” *Christopher v. SmithKline Beecham Corp.*, 132 S. Ct. 2156, 2168 (2012). FDA’s theory would mean that the innumerable laboratories that have openly bypassed FDA’s device regulations over the past four decades, and the countless doctors who have widely employed such “unapproved devices” in diagnosing and treating individual patients, have been spared criminal penalties only by the grace of a decades-long exercise of enforcement discretion. Where a federal agency has “never initiated any enforcement actions ... or otherwise suggested that it thought the industry was acting unlawfully,” it is highly unlikely that the industry has been operating unlawfully for decades—instead, “the ‘more plausible hypothesis’ is that the [agency] did not think the industry’s practice was unlawful.” *Id.* (quoting *Yi*, 480 F.3d at 510-511). Any construction of the FDCA that would render thousands of CMS- and state-regulated laboratories and hundreds of thousands of doctors a professional class of unwitting, unprosecuted violators of federal criminal law rests on a highly implausible interpretation of what Congress did and what it intended and must accordingly be rejected.

D. FDA’s Interpretation Is Foreclosed By The Broader Regulatory Scheme

The FDCA itself makes plain that laboratory-developed testing services do not fall within FDA’s delegated authority. Where “the intent of Congress is clear and unambiguously expressed by the statutory language at issue, that [is] the end of our analysis.” *Zuni Pub. School Dist. No. 89 v. Dep’t of Educ.*, 550 U.S. 81, 93–94 (2007). Nonetheless, here, “the broader context of the [statutory scheme] as a whole,” *Robinson v. Shell Oil Co.*, 519 U.S. 337, 341 (1997), makes crystal clear what is already evident from the face of the FDCA: Congress’ enactment of CLIA’s 1988 amendments leaves no doubt that the FDCA does not bear the weight of FDA’s reading. That is, there is no need to speculate as to why Congress did not bring laboratory-developed testing services under FDA’s authority in the FDCA. When Congress expressly considered and addressed

the unique issues posed by laboratory-developed testing services, it opted to do so in a different statute (CLIA) administered by a different agency (CMS).

Clinical laboratories have been regulated by the federal government in various ways, going back to at least 1967, and yet at no time was there any suggestion of the FDA's ability to regulate laboratory-developed testing services. For example, laboratories engaged in interstate commerce were initially regulated under the Clinical Laboratory Improvement Act of 1967. Pub. L 90-174, 81 Stat. 536 (1967). At the same time, laboratories participating in Medicare also had to meet separate regulatory requirements established in Medicare's Conditions of Participation or Conditions of Coverage applicable to the particular type of laboratory involved. *See* Medicare, Medicaid and CLIA Programs; Revision of the Laboratory Regulations for the Medicare, Medicaid, and Clinical Laboratories Improvement Act of 1967 Programs, 55 Fed. Reg. 9538-39. However, there is nothing in those regulations to suggest that FDA, rather than CMS (referred to then as HCFA, the Health Care Financing Administration) had authority over laboratory-developed testing. In fact, when HCFA revised the Medicare and 1967 CLIA regulations in 1990, it noted that FDA *did* have authority over blood bank programs, but made no mention of authority over laboratory-developed testing services. *Id.*

In CLIA's 1988 amendments—passed 12 years after the 1976 MDA—Congress created an even more detailed statutory framework specifically to govern clinical laboratories and their tests. Congress centralized oversight, moreover, under the auspices of HHS (in turn, CMS)—*not* FDA. CLIA requires the certification of clinical laboratories, defined as any facility for “examination of materials derived from the human body for the purpose of providing information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings.” 42 U.S.C. §263a(a). CLIA prohibits these laboratories from soliciting or accepting specimens for laboratory tests until the laboratories are CMS-certified. *Id.* §263a(b). CLIA further provides that CMS “shall issue standards” to ensure quality control, including standards “adequate and appropriate for the validity and reliability of the laboratory examinations” and standards for the personnel “qualifications . . . for the direction, supervision, and performance of examinations and procedures within the laboratory.” *Id.* §263a(f)(1)(A), (C). CLIA also requires laboratories to participate in regular “proficiency testing.” *Id.* §263a(f)(1)(D).

The very enactment of the CLIA amendments in 1988 would be well-nigh inexplicable if Congress had intended in the 1976 MDA, as FDA asserts, to subject laboratory-developed testing services to the FDCA's device regulations. Under FDA's theory, by the time Congress amended CLIA in 1988, FDA *already* had authority to regulate *the very same tests*—authority that it was simply declining in its discretion to exercise. But that theory cannot be sustained without rendering CLIA utterly pointless. Instead, Congress passed the CLIA amendments precisely because Congress did not share FDA's interpretation of the MDA.

Indeed, neither CLIA's statutory text nor legislative history in 1988 makes any reference to preexisting FDA authority to regulate laboratory-developed testing services, let alone the sweeping authority to regulate such services as “medical devices.” Since Congress was prompted to action by concerns about the inadequate regulation of pap testing (a laboratory-developed testing service), if FDA possessed pre-existing authority that it had failed to tap, there is little doubt that FDA officials would have been in the proverbial “hot seat” before Congress. Instead, FDA was unmentioned.

Making the absence of FDA references all the more noteworthy, Congress' avowed objective in CLIA's 1988 amendments was to replace the “patchwork of inconsistent and overlapping standards” regulating clinical laboratories to date with a “unified regulatory mechanism.” S. Rep. No. 100-561, at 3 (1988); H.R. Rep. No. 100-899, at 12 (1988); *see also* 134 Cong. Rec. 23606 (1988) (statement of Rep. Dingell) (“The legislation essentially directs the

Department of Health and Human Services to regulate all laboratories *under a single statute*. It should end duplicative and confused regulation under a tangled web of statutory authorities.”). Accordingly, the legislative history is replete with references to the overlapping standards of CLIA, of the Medicare statute, and of state regulation—but strikingly devoid of any references to FDA or the FDCA. For instance, the House Report stated that clinical laboratories had, to date, been “governed by two separate and distinct statutes, *Medicare and CLIA*,” and included a section entitled “Current Regulatory System” that contained no mention whatsoever of FDA. H.R. Rep. No. 100-899, at 11-12 (1988). Thus, even as Congress took deliberate steps to streamline and strengthen federal regulations over clinical laboratory testing, it made no acknowledgement of any parallel FDA standards.

In fact, Congress armed CMS with enforcement authorities under CLIA that, on FDA’s theory, would be wholly redundant with FDA’s enforcement authorities under the FDCA. For instance, CLIA requires laboratories to submit to inspections of their “facilities, equipment, materials, records, and information” to verify compliance with CMS standards, 42 U.S.C. §263a(g)—a provision that, on FDA’s reading, would be rendered superfluous by FDCA’s requirement that device establishments submit to inspections, 21 U.S.C. §374(a)(1)(B).

Worse still, CMS laboratory test regulations would *conflict* with FDA device regulations. CMS, for example, has distinguished laboratory tests that use FDA-approved products from laboratory tests that use products that have not undergone the FDA approval process. For the latter, CMS requires enhanced performance specifications, obligating laboratories to establish every test system’s “analytical sensitivity,” “analytical specificity to interfering substances,” and other additional performance characteristics “before reporting patient test results.” 42 C.F.R. §493.1253(b)(2). Any FDA guidance requiring this latter category to undergo premarket device approval processes would thus be flatly irreconcilable with the prescriptions in §493.1253(b)(2). Similarly, CMS allows laboratories to continually update their tests to reflect new scientific developments as long as they appropriately validate and document any modifications. But FDA’s device regulations would, in sharp contrast, require supplemental filings and FDA authorizations for any and all modifications—an utterly impractical mandate given the constantly evolving and dynamic nature of laboratory-developed testing services.

In sum, CLIA’s 1988 amendments leave no doubt that Congress intended *not* to regulate laboratory-developed testing services in the 1976 MDA. To the extent more regulation is required, CLIA makes clear that Congress’ approach has been to enhance oversight by CMS, not to grant new and duplicative authority to FDA.

E. Even If The FDCA Were Ambiguous, FDA’s Interpretation Would Be Objectively Unreasonable

FDA’s view that laboratory-developed testing services can be regulated as medical “devices” is “clearly contrary to the intent of Congress.” *Edward J. DeBartolo Corp. v. Fla. Gulf Coast Bldg. & Constr. Trades Council*, 485 U.S. 568, 574 (1988). In any event, even if there were some ambiguity in the FDCA, FDA’s view would be an objectively unreasonable and substantively indefensible interpretation of the statute. It would mean that Congress, in exceptionally cryptic fashion, rendered *all* laboratory-developed testing services (if not *all* services that utilize a medical device) unapproved medical devices, even though such services do not entail any physical product. It would mean that Congress did so in a statute that was concerned with the “commercial distribution” of mass-produced physical articles moving in interstate commerce, when individualized in-house laboratory tests never even leave the confines of the laboratory, let alone move across state borders—and when Congress specifically addressed the entirely distinct issues of clinical laboratory tests in a wholly different statute, CLIA, overseen by a different agency, CMS. And it would mean that Congress, in the FDCA, interfered with the

practice of medicine in contravention of the FDCA’s own explicit disclaimer of such intent. That far-fetched interpretation of Congress’ actions cannot withstand scrutiny. *See Commissioner v. Brown*, 380 U.S. 563, 571 (1965) (courts have “some scope for adopting a restricted rather than a literal or usual meaning of [statute’s] words where acceptance of that meaning would lead to absurd results”).

In fact, construing the FDCA to authorize FDA’s regulation of and interference with the practice of medicine and the doctor-patient relationship could well raise nettlesome constitutional questions both about federal intrusion into the medical domain and about heavy-handed governmental regulation of a sensitive personal and professional relationship. *See, e.g., Rust v. Sullivan*, 500 U.S. 173, 200 (1991) (“It could be argued by analogy that traditional relationships such as that between doctor and patient should enjoy protection under the First Amendment from Government regulation....”); *Colautti v. Franklin*, 439 U.S. 379, 387 (1979) (citing “the central role of the physician” and “the importance of affording the physician adequate discretion in the exercise of his medical judgment”); *Planned Parenthood of Central Mo. v. Danforth*, 428 U.S. 52, 67 n. 8 (1976) (condemning regulations tending to “confine the attending physician in an undesired and uncomfortable straitjacket in the practice of his profession”). FDA should avoid any interpretation that raises such constitutional questions. The doctrine of “[c]onstitutional avoidance trumps even *Chevron* deference, and easily outweighs any lesser form of deference [a court] might ordinarily afford an administrative agency.”⁵

As a practical matter, moreover, FDA is manifestly not equipped to bear the massive regulatory burden it claims that Congress intended it to shoulder. FDA has projected that it would take nearly *a decade* for it to phase in its asserted regulatory authority over laboratory-developed testing services. That it would take that many years to handle the full scope of the administrative responsibilities it asserts is yet another indication that Congress never intended for FDA’s preexisting (and ill-suited) regulations over drugs and devices in interstate commerce to sweep in laboratory-developed testing services. Just last Term, the Supreme Court rejected a similar effort by a federal agency to claim newfound regulatory authority in ways that would overburden the agency’s resources. *See Util. Air Regulatory Grp.*, 134 S. Ct. at 2444. As the Court explained, the fact that an expansive interpretation of regulatory authority “would place plainly excessive

⁵ *Union Pac. R.R. Co. v. U.S. Dep’t of Homeland Sec.*, 738 F.3d 885, 893 (8th Cir. 2013) (discussing *Chevron U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984)); *see also Edward J. DeBartolo Corp. v. Florida Gulf Constr. Coast Bldg. and Trades Council*, 485 U.S. 568, 574-75 (1988) (noting that a “statutory interpretation by the Board would normally be entitled to deference” but not deferring to the Board’s interpretation because it would raise a serious constitutional issue that could be avoided through an alternative interpretation); *see also Solid Waste Agency of N. Cook Cty. v. U.S. Army Corps of Eng’r*, 531 U.S. 159, 174 (2001) (court chose to “read the statute as written to avoid the significant constitutional and federalism questions raised by [the Army Corps of Engineers’] interpretation, and therefore [to] reject the request for administrative deference”); *U.S. West, Inc. v. FCC*, 182 F.3d 1224, 1231 (10th Cir. 1999) (“[I]f we determine that [agency’s] rule presents a serious or grave constitutional question, we will owe the [agency] no deference, even if its . . . regulations are otherwise reasonable, and we will apply the rule of constitutional doubt.”); *Campbell on Behalf of Campbell v. Shalala*, 1994 WL 163719, at *4 (D. Me. Mar. 16, 1994) (“Such an interpretation of the Secretary’s income counting provisions [in agency regulations] is obviously to be avoided,” because it “would implicate Fifth Amendment equal treatment concerns.”); *Moreland v. Sullivan*, 765 F. Supp. 970, 975 (C.D. Ill. 1991) (“The court is aware that it generally must defer to an administrative agency’s interpretation of its own regulations. Yet the court is also aware that it must avoid a regulatory interpretation that presents serious constitutional difficulties.”).

demands on limited government resources is alone a good reason for rejecting it.” *Id.* But the agency’s felt need to impose limits on its newly-claimed jurisdiction—limits found nowhere in the statute itself—to make the program administrable provides further evidence that the agency has exceeded its statutory authority. *See id.* at 2446 (“We are not willing to stand on the dock and wave goodbye as [the agency] embarks on this multiyear voyage of discovery.”).

Indeed, “[t]hree recent studies” from the FDA Science Board, the National Academies Institute of Medicine, and the GAO have all concluded that FDA “suffers from serious scientific deficiencies and is not positioned to meet current or emerging regulatory responsibilities” and “lacks the resources needed to accomplish its large and complex mission.” *Wyeth v. Levine*, 555 U.S. 555, 578 n.11 (2009). A former FDA chief counsel has observed that FDA suffers from “the hollow government syndrome—an agency with expanded responsibilities, stagnant resources, and the consequent inability to implement or enforce its statutory mandates.” Peter Barton Hutt, *The State of Science at the Food and Drug Administration*, 60 ADMIN. L. REV. 431, 431 (2008). An FDA advisory panel has observed that, since 1938, when the FDCA was enacted, Congress has adopted “125 statutes that directly impact FDA’s regulatory responsibilities,” by requiring “the development of implementing regulations, guidance or other types of policy, and some require the establishment of entire new regulatory programs.” FDA Science Board, *FDA Science and Mission at Risk: A Report of the Subcommittee on Science and Technology* §2.1 (2007). Virtually all of those statutory mandates “require some type of scientific knowledge or expertise for the agency to address them.” *Id.* The report found that, despite the addition of all of these requirements, Congress has not provided “an appropriation of new personnel and increased funding designed to allow adequate implementation.” *Id.* The report concluded that “[t]he scientific demands on the Agency far exceed its capacity to respond” and that FDA has “serious scientific deficiencies and is not positioned to meet current or emerging regulatory responsibilities.” *Id.*, at §1.1, pp. 2-3.

FDA’s proposed actions, moreover, would have numerous adverse public health repercussions fundamentally inconsistent with its mission. As an initial matter, FDA oversight of laboratory-developed testing services would sharply curtail the number and range of tests available to doctors and their patients. Currently, a wide swath of critical diagnostic tests are available only as in-house laboratory tests, including many “gold standard” DNA sequencing assays, newborn screening tests, and tests for rare diseases. The prohibitive costs of obtaining FDA premarket clearance or approval for each such test would leave many laboratories unable to continue offering them, despite patient need and physician demand. Even where supported by well-accepted, peer-reviewed research and scientific studies, “low-volume” tests designed for individual patients or small patient populations often generate only modest financial returns for laboratories. In turn, the patients who benefit from the valuable clinical information generated by these tests would be left with no alternatives.

FDA oversight would also render critical testing, particularly for patients with emergent infectious diseases, unavailable in the “lag time” before FDA approval. The FDA approval process is protracted and not designed for the rapid clearance of tests. Many clinical laboratories track world trends regarding infectious diseases and have demonstrated immediate or near-immediate responses to infectious diseases ranging from SARS to H1N1 and Avian Influenza. In these fast-moving, life-or-death situations, awaiting the development of manufactured test kits and the completion of FDA’s clearance procedures could entail potentially catastrophic delays, with disastrous consequences for patient care.

In the long run, moreover, FDA oversight would stunt and stifle innovation and competition in the diagnostic testing field. Laboratory tests are constantly evolving in response to scientific advances. Laboratories continually develop, refine, and validate their tests to ensure

that they reflect the most up-to-date scientific literature and advanced diagnostic testing technologies. Furthermore, laboratories routinely modify FDA-approved and FDA-cleared *in vitro* diagnostic test kits in order to improve performance, expand diagnostic capabilities, or to incorporate the latest scientific research and discoveries to benefit patients. Regulating laboratory-developed testing services as devices, however, would dramatically slow not only the initial premarket approval of new tests, but also improvements to existing tests, delaying access to new and improved diagnostic testing services for patients and clinicians. In the long run, such regulation would impede clinical laboratories' ability to meet public health needs.

* * *

In sum, FDA's asserted jurisdiction over laboratory-developed testing services lacks any statutory basis and embodies a misguided attempt to fit a square peg in a round hole. FDA's strained reading of its preexisting authority under the FDCA defies bedrock principles of statutory interpretation, common sense, and longstanding industry practice. Indeed, the FDCA—a statute targeted at mass-produced, mass-marketed, and mass-distributed drugs and devices moving in interstate commerce—is a poor fit for the distinct issues raised by laboratories that provide vital diagnostic tools for doctors as part and parcel of the practice of medicine. And this is not just a question of FDA attempting to fill a regulatory gap or administer a statute in the face of congressional silence. The more fundamental problem is that Congress has *already* considered the distinct issues raised by laboratory-developed testing services in CLIA, and chose to address those issues by vesting regulatory authority *not* in FDA, but in CMS. CLIA thus reflects Congress' clear and unmistakable intent to regulate laboratory-developed testing services under a statutory framework that is emphatically *not* the FDCA.

FDA's theory, moreover, necessarily implies that the entire laboratory industry (and the entire medical profession that has outsourced diagnostic tests to those laboratories) has operated for decades as a professional class of unwitting, unprosecuted violators of federal criminal laws. It renders inexplicable FDA's decades-long purported exercise of enforcement discretion, as FDA, by its own admission, has *never* before sought to enforce the FDCA laws against clinical laboratories. And it means that FDA itself will require nearly a full decade to restore "law and order" to that industry, and adapt to the enormous administrative burdens that its asserted jurisdiction would entail. Those implausible implications make plain that FDA's power grab does not effectuate, and instead flouts, Congress' intent.

III. FDA MAY NOT REGULATE LABORATORY-DEVELOPED TESTING SERVICES BY MEANS OF "GUIDANCE" DOCUMENTS RATHER THAN NOTICE-AND-COMMENT RULEMAKING

The FDCA as it now stands does not permit FDA to regulate laboratory-developed testing services, and FDA has not gone to Congress to seek the dramatic overhaul and fundamental redirection of the FDCA that such action would necessitate. But the problems with FDA's attempt to regulate laboratory-developed testing services do not end there. FDA has also failed to undertake the notice-and-comment procedures that would be required to create the binding rules that it seeks to impose, even if it had the statutory authority to do so. That is, FDA has bypassed not only Congress and its plan for regulating this vital area of public health but also proper rulemaking procedures, seeking impermissibly—and in defiance of the framework established by Congress as long ago as 1946 to subject the administrative state to the rule of law—to enlarge its control over laboratory-developed testing services through mere informal "Guidance" documents.

A. FDA's "Guidance" Imposes Binding, Substantive Obligations on Private Parties

FDA has issued so-called Guidance documents that go well beyond providing helpful guidance. Instead, they seek to impose significant, binding requirements on private parties that provide laboratory-developed testing services. The Guidance announces a risk-based, phased-in approach to a “Framework for Regulatory Oversight of Laboratory Developed Tests.” The main elements of the Framework include extensive obligations that laboratories must observe in order to comport with numerous medical device regulations. As detailed above, *see supra* at 6, these obligations include: giving notification to FDA about, or registering and listing of, laboratory-developed testing services (and “significantly” changed laboratory-developed testing services) under 21 C.F.R. §807; classifying services by risk levels and assisting FDA in determining what premarket review requirements to enforce against which tests; reporting of “adverse events” under 21 C.F.R. §803.50; submitting to premarket review “high-risk” and “moderate-risk” laboratory-developed testing services to assess their clinical validity, *see* 21 C.F.R. §814; and complying with Quality System Regulations, including 21 C.F.R. §820.30(a)-(j).

These requirements are highly burdensome, and FDA’s effort to impose them by means of Guidance documents—without undertaking full notice and comment rulemaking—is an improper end run around its procedural obligations. Under the Administrative Procedure Act, an agency generally may issue “interpretive rules” and “general statements of policy” without notice and comment, but that is not the case for “substantive” rules. As the Act makes clear, an agency’s “substantive” rules are valid only if they are promulgated after proper notice and comment. *See* 5 U.S.C. §553.⁶ Here, for several reasons, FDA’s Guidance announces substantive rules subject to notice and comment.

To begin with, FDA’s Guidance has precisely the purpose and effect that characterizes a substantive legal rule rather than a merely helpful hint or a useful piece of advice: it “purports to impose legally binding obligations or prohibitions on regulated parties” and forms “the basis for an enforcement action.” *Nat’l Min. Ass’n*, 758 F.3d at 251.⁷ Specifically, FDA is seeking to establish a new “Framework for Regulatory Oversight” of clinical laboratories, which will saddle laboratories with binding legal obligations that have never before been applied to them. As a result, FDA’s actions will have dramatic effects on the way in which clinical laboratories operate. *See General Electric v. EPA*, 290 F.3d 377, 382 (D.C. Cir. 2002) (agency action with “binding effects on private parties or the agency itself with the ‘force of law’” is a substantive rule); *Nat’l Family Planning & Reprod. Health Ass’n v. Sullivan*, 979 F.2d 227, 238–39 (D.C. Cir. 1992) (rulemaking required when interpretation “produce[s] significant effects on private interests”). FDA’s pronouncements thus plainly amount to “lawmaking,” the hallmark of a substantive rule.⁸

⁶ FDA’s Guidance clearly meets the APA’s broad definition of a “rule”—an agency statement with “future effect” that is “designed to implement, interpret, or prescribe law or policy” or prescribe FDA’s “procedure, or practice.” 5 U.S.C. §551(4).

⁷ By contrast, an *interpretive* rule “merely interprets a prior statute or regulation, and does not itself purport to impose new obligations or prohibitions or requirements.” *Nat’l Min. Ass’n*, 758 F.3d at 251. Thus, an interpretive rule involves no “lawmaking” or “change in the legal norm.” *Syncor*, 127 F.3d at 94.

⁸ FDA’s inability to ground its regulation in the language of the FDCA is a further indication that it is making new law. Courts have noted that “[t]he distinction between an interpretative rule and substantive rule ... likely turns on *how tightly the agency’s interpretation is drawn linguistically* from the actual language of the statute,” *Paralyzed Veterans v. D.C. Arena L.P.*, 117 F.3d 579, 588 (D.C. Cir. 1997) (emphasis added), with a rule that is largely untethered to the statutory text falling on the substantive side of the line. Here, FDA’s strained interpretation equating laboratory-developed testing services to “devices” is certainly not obvious from, or

For the same reasons, FDA’s Guidance cannot be viewed merely as a “general statement of policy” that “explains how the agency ... will exercise its broad enforcement discretion or permit discretion under some extant statute or rule.” *Nat’l Min. Ass’n v. McCarthy*, 758 F.3d 243, 252 (D.C. Cir. 2014). The defining feature of a true policy statement is that it is “binding on neither the public ... nor the agency” and “does not affect the legal norm.” *Syncor Int’l Corp. v. Shalala*, 127 F.3d 90, 94 (1997). It “imposes no obligations or prohibitions on regulated entities,” such that they “may ignore the ... Guidance without suffering any legal penalties or disabilities.” *Nat’l Min. Ass’n*, 758 F.3d at 252-53. Here, FDA’s Guidance imposes binding norms, with no real basis in the statute. Read as a whole, this purported “guidance” does much more than guide: “[i]t commands, it requires, it orders, it dictates.” *Appalachian Power Co. v. EPA*, 208 F.3d 1015, 1023 (D.C. Cir. 2000). Laboratories are now *obligated* to notify FDA of each laboratory-developed test and to provide basic information within 6 months of the final guidance. Laboratories are *obligated* to comply with FDA’s risk classification and to seek premarket approval of “high risk” tests. And there is no question that FDA will bring enforcement actions and penalties against laboratories if they do not comply.

Although FDA has claimed that, by issuing its Guidance, it is doing no more than announcing a revised enforcement policy regarding laboratory-developed testing services, *see* 79 Fed. Reg. at 59778 (“guidance ... does not create or confer any rights for or on any person and does not operate to bind FDA or the public”), the “label an agency attaches to its action is not determinative.” *Continental Airlines, Inc. v. CAB*, 522 F.2d 107, 124 (D.C. Cir. 1974); *see also Appalachian Power Co.*, 208 F.3d at 1024 (“an agency may not escape the notice and comment requirements ... by labeling a major substantive legal addition to a rule a mere interpretation”). To the contrary, “it is the substance of what the [agency] has purported to do and has done which is decisive.” *Chamber of Commerce v. Occupational Safety & Health Admin.*, 636 F.2d 464, 468 (D.C. Cir. 1980); *see also General Electric*, 290 F.3d at 383 (agency action requires rulemaking if it is “binding as a practical matter,” regardless of agency’s self-serving characterization).⁹ Here, the substance of FDA’s actions—imposing a host of new mandatory obligations on laboratory-developed testing services—makes clear that it has gone well beyond simply stating its non-binding views about proper enforcement policy. A mere declaration by the agency to the contrary is not enough to change that basic fact.

Finally, FDA’s foray into impermissible lawmaking is further demonstrated by the fact that its Guidance would fundamentally rewrite longstanding FDA regulations with respect to registration under the FDCA. FDA’s existing regulations—first promulgated in 1977 after notice-and-comment rulemaking—have consistently stated that private entities need not comply with the

compelled by, the FDCA’s very general language. *See Catholic Health Initiatives v. Sebelius*, 617 F.3d 490, 494 (D.C. Cir. 2010) (agency can avoid rulemaking only if “interpretation” flows from a “document whose meaning compels or logically justifies the proposition”). Indeed, that interpretation is all but foreclosed by the ordinary understanding of the FDCA’s terms.

⁹ Numerous courts have rejected agencies’ self-interested attempts to recharacterize substantive rules as mere interpretations. *See CropLife Am. v. EPA*, 329 F.3d 876, 881, 883 (D.C. Cir. 2003) (press release announcing that agency would no longer consider or rely on third-party human studies was binding regulation, rather than a mere policy statement, because it “reflects an obvious change in established agency practice,” “creates a ‘binding norm,’” and “clearly establishes a substantive rule”); *Barrick Goldstrike Mines Inc. v. Browner*, 215 F.3d 45, 47-49 (D.C. Cir. 2000) (guidance document was binding because it created “legal consequences” and “the prospect of hardship”); *Alaska Prof’l Hunters Ass’n, Inc. v. FAA*, 177 F.3d 1030, 1034 (D.C. Cir. 1999) (new rule announcing that fishing and hunting guides long exempt from commercial pilot restrictions would now be required to comply with such restrictions was substantive).

FDCA's device-registration requirements if their "major responsibility is to render a service necessary to provide the consumer (*i.e.*, patient, physician, layman, etc.) with a device or the benefits to be derived from the use of a device; for example, a ... *clinical laboratory*." 21 C.F.R. §807.65(i); *see also* 21 C.F.R. §807.65(f) (exempting from registration persons who "do not introduce such devices into *commercial distribution*") (emphasis added). Moreover, the regulations explicitly set forth the *reason* that clinical laboratories (including those engaged in laboratory-developed testing services) are exempted from registration: the fact that "such registration is not necessary for the protection of the public health." 21 C.F.R. §807.65(i). Thus, FDA has long advised laboratories that they could meet their regulatory responsibilities without complying with the FDCA's device regulations. And, based on that settled understanding of the law, clinical laboratories have invested billions of dollars in developing innovative new testing services.

FDA's present about-face, therefore, upends nearly four decades of established practice. While an agency is not prohibited from changing its position, "recourse to notice-and-comment rulemaking" is a critical safeguard against the risk of unfair surprise for regulated parties. *Long Island Care at Home, Ltd. v. Coke*, 551 U.S. 158, 170-71 (2007); *see also Christopher*, 132 S. Ct. at 2168-69 (recognizing "potential for unfair surprise" when Labor Department's "announcement of its interpretation [wa]s preceded by a very lengthy period of conspicuous inaction" with "no [notice or] opportunity for public comment"). FDA's "current doubts about the wisdom of the regulatory system followed ... for more than thirty years does not justify disregarding the requisite procedures for changing that system." *Alaska Prof. Hunters Ass'n Inc. v. FAA*, 177 F.3d at 1035. Here, all of the reasons that FDA has advanced for its proposed change—the expanding importance of diagnostic tests in clinical decision making, the growing complexity of laboratory-developed testing services, and the increasing number of corporations in the industry—"are exactly the sorts of changes in fact and circumstance which notice-and-comment rulemaking is meant to inform." *Syncor*, 127 F.3d at 95. And the circumstantial nature of those reasons make clear that FDA has introduced "not a change in interpretation or in enforcement policy, but rather ... [a] fundamentally new regulation." *Id.*

B. FDA May Not Circumvent the Requirements of Rulemaking By Using a "Guidance" Document Instead

FDA may not use the "Guidance" process to avoid the vital protections guaranteed for nearly seven decades by the APA. In fact, FDA has attracted widespread criticism from Congress and commentators for its use of guidance documents as "a backdoor approach" to "sacrifice[] the procedural safeguards dictated" by the APA and "secure[] widespread adherence to its technically nonbinding policies." Lars Noah, *Governance by the Backdoor: Administrative Law(lessness?) at the FDA*, 93 NEB. L. REV. 89, 90 (2014).¹⁰ A congressional oversight committee, moreover, recently charged that "draft guidances are becoming default FDA policy." *GOP Senators Criticize FDA Delays in Finalizing Draft Guidances*, Drug Indus. Daily, May 9, 2014, available at 2014

¹⁰ *See also* Todd D. Rakoff, *The Choice Between Formal and Informal Modes of Administrative Regulation*, 52 ADMIN. L. REV. 159, 168 (2000) ("there has been a striking increase in the number of FDA-issued documents intended to give guidance to the regulated industry but not adopted through public procedures"); Lars Noah, *The Little Agency That Could (Act with Indifference to Constitutional and Statutory Strictures)*, 93 CORNELL L. REV. 901, 924 (2008) ("FDA evidently has institutionalized a practice of cavalierly ignoring legal constraints"); Kasey L. Martini, *A Historical Look at FDA's Approach to Regulation and Policymaking* (2009), available at <http://nrs.harvard.edu/urn-3:HUL.InstRepos:10139281> ("it is arguable that the FDA has developed and expanded the use of guidance as an alternative to notice and comment rulemaking more so than any other agency").

WLNR 12430760. As one FDA official has noted, proceeding by rulemaking is “a huge ordeal ... there are economic analyses of the impact [of the proposed regulation], notice and comment, involvement of [the Office of Management and Budget], etc.” See Erica Seiguer & John J. Smith, *Perception and Process at the Food and Drug Administration: Obligations and Trade-Offs in Rules and Guidances*, 60 Food & Drug L.J. 17, 24 (2005). But that “ordeal” is intentionally rigorous: FDA has a bedrock obligation to meaningfully consider and respond to comments and undertake economic analysis of the regulatory impact of its proposed action.

1. FDA May Not Use “Guidance” Documents To Evade the APA’s Notice-and-Comment Requirements

The APA establishes notice-and-comment procedures requiring an agency to “consider[]” the comments submitted to it. See 5 U.S.C. § 553(c). “Section 553 requires consideration of whatever data and views are submitted. Such consideration has been considered [necessary] to demonstrate an ‘open mind.’” *Mortgage Investors Corp. of Ohio v. Gober*, 220 F.3d 1375, 1379 (Fed. Cir. 2000). The requirement to consider public comment is no mere formality. Rather, it is “designed to assure due deliberation,” *Smiley v. Citibank (South Dakota), N.A.*, 517 U.S. 735, 741 (1996), which in turn is essential to “informed administrative decisionmaking.” *Chrysler Corp. v. Brown*, 441 U.S. 281, 316 (1979). A mandate that an agency be required to consider comments is critical, “because the concern is that an agency is not likely to be receptive to suggested changes once the agency puts its credibility on the line” *Advocates for Highway & Auto Safety v. Federal Highway Admin.*, 28 F.3d 1288, 1292 (D.C. Cir. 1994).

Closely related to the requirement that the agency consider comments is the rule that it meaningfully respond to relevant and significant ones. Thus, “[t]he requirement that agency action not be arbitrary or capricious includes a requirement that the agency adequately explain its result and respond to relevant and significant public comments.” *Pub. Citizen, Inc. v. FAA*, 988 F.2d 186, 197 (D.C. Cir. 1993) ; see also *Home Box Office, Inc. v. FCC*, 567 F.2d 9, 35-36 (D.C. Cir.), cert. denied, 434 U.S. 829 (1977) (“[T]here must be an exchange of views, information, and criticism between interested persons and the agency. . . . Moreover, a dialogue is a two-way street: the opportunity to comment is meaningless unless the agency responds to significant points raised by the public.”).

These requirements have real teeth. Numerous courts have set aside actions by agencies for failing to adequately consider or respond to comments.¹¹ FDA rulemakings often result in changes to proposed rules. And numerous studies have shown that a significant proportion of proposed rules—approaching 40%—are “withdrawn in whole or in part because of the receipt of some significant adverse comment.” Noah, 93 NEB. L. REV. at 96.

FDA’s Guidance bypasses the APA’s well-established notice-and-comment procedures. Instead, it was issued consistent with FDA’s so-called “good guidance practices” regulation. See 21 C.F.R. §10.115; 79 Fed. Reg. at 59778 (Oct. 3, 2014). Although FDA is nominally accepting

¹¹ E.g., *Cape Cod Hosp. v. Sebelius*, 630 F.3d 203, 211 (D.C. Cir. 2011) (vacating challenged rules because agency failed to provide a reasoned response to the hospitals’ comments); *Louisiana Federal Land Bank Ass’n, FLCA v. Farm Credit Admin.*, 336 F.3d 1075, 1080-81 (D.C. Cir. 2002) (remanding challenged rule because of agency’s failure to respond to comment); *Fox Television Stations, Inc. v. FCC*, 280 F.3d 1027, 1050–51 (D.C. Cir. 2002) (holding that FCC’s failure to consider and respond to three arguments raised by commenter required that regulations be vacated), modified on reh’g, 293 F.3d 537 (D.C. Cir. 2002); *Nehemiah Corp. of America v. Jackson*, 546 F.Supp.2d 830, 842-43 (E.D. Cal. 2008) (holding that agency failed to respond to two categories of comments and setting aside challenged rule).

public comments on the Guidance documents, there is an important distinction between “good guidance practices” and APA rulemakings: the guidance regulation provides merely that FDA will *review* comments received and prepare a final version that “incorporates suggested changes, when appropriate.” 2 C.F.R. §10.115(g)(1)(iv). FDA is thus left to decide on its own what is “appropriate,” and it is not required to *respond* to significant comments. K.M. Lewis, *Informal Guidance and the FDA*, 66 Food & Drug L.J. 507, 522 (2011). The absence of a *mandate* to consider comments makes a critical difference. In the rulemaking context, it is firmly established that “[c]onsideration of comments as a matter of grace is not enough.” *McLouth Steel Products Corp. v. Thomas*, 838 F.2d 1317, 1323 (D.C. Cir. 1988). That is all FDA offers here, and experience shows that it is inadequate. “[E]ven though FDA accepts comments from the public [with respect to a guidance document] ... it is very unusual for FDA to actually change its position or incorporate any of the feedback into the guidance.” K.M. Lewis, *Informal Guidance and the FDA*, 66 Food & Drug L.J. 507, 522 n.142 (2011).

2. FDA May Not Use “Guidance” Documents To Avoid Considering the Enormous Economic Impact of its Proposal.

In addition, APA rulemakings are subject to Executive Orders mandating that federal regulations be cost-effective, evidence-based, and compatible with economic growth, innovation, job creation, and competitiveness.¹² However, the FDA Guidance documents in this proceeding do not consider the cost and economic impact of the proposed extension of FDA jurisdiction over clinical laboratories. Further, the extent to which the Office of Management and Budget (OMB) reviews guidance documents is “unclear” at best, and even in the relatively rare instances where that review does occur, there is a “significant question . . . whether the use of guidance documents might allow agencies to avoid [the] disciplining requirements,” such as cost-benefit analysis, “that would otherwise have applied through the regulatory review process.”¹³ This process is an important way of ensuring agency accountability. See Elena Kagan, *Presidential Administration*, 114 HARV. L. REV. 2245, 2286-87 (2001).

The absence of an economic impact analysis is a particularly glaring omission given the sweeping practical effects of FDA’s radical change in policy. As noted, FDA’s assertion of jurisdiction will significantly burden clinical laboratories, superimposing a duplicative bureaucratic regime on a vibrant and constantly evolving laboratory testing industry that is already closely regulated under CLIA, and that FDA has no prior experience in regulating. FDA, moreover, has failed to explain how the current CMS regulations and FDA’s proposed framework would work together in practice, raising numerous open questions that would be best resolved through a full airing of comments. For example, how would inspections and quality control procedures operate, if FDA and CMS have different rules and requirements? What is the “label” on an LDT, since no physical item is actually being distributed to which a label could be applied? How would FDA’s existing “adverse event” and “device malfunction” reporting requirements apply to laboratory-developed testing services? What does it mean to say that a test “malfunctioned”? Are laboratory-developed testing services subject to the medical device tax

¹² See Regulatory Planning and Review, Exec. Ord. No. 12866, 58 Fed. Reg. 51735 (Sept. 30, 1993); Improving Regulation and Review, Exec. Ord. No. 13563, 76 Fed. Reg. 3821 (Jan. 18, 2011).

¹³ Nina A. Mendelson & Jonathan B. Wiener, *Responding to Agency Avoidance of OIRA*, 37 HARV. J.L. & PUB. POL’Y 447, 487, 489 (2014); see also *id.* at 485-89; Nina A. Mendelson, *Regulatory Beneficiaries and Informal Agency Policymaking*, 92 CORNELL L. REV. 397, 411 & n. 80 (2007); Lars Noah, *Governance by the Backdoor: Administrative Law(lessness?) at the FDA*, 93 NEB. L. REV. 89, 111-12 (2014) (noting that OMB review of guidance documents is uncertain).

under the Affordable Care Act? Would laboratory consultations be considered “off-label promotion”? The practical implications of FDA’s proposal are left largely unexplored.

Economic impact analysis is essential here, moreover, where the regulatory burdens on FDA will be daunting. There are more than 11,000 laboratories currently permitted to use and develop laboratory-developed testing services, and there may be more than 100,000 laboratory-developed testing services. Under the Guidance, every laboratory developing and performing LDTs will be required to “notify” FDA that it is performing a laboratory-developed test and provide extensive information about each laboratory-developed test being offered by that laboratory within 6 months of the issuance of the final guidance. By comparison, last year, FDA approved 21 Pre-Market Submissions for all medical devices, only 4 of which were for *in-vitro* diagnostic test kits. And FDA is proposing this enormous expansion of its regulatory responsibilities at a time when it is facing severe resource constraints—a reality that FDA implicitly recognizes by giving itself nearly *a decade* to implement its new regulatory scheme. This is hardly the time for FDA to take on a vast new regulatory task at all, much less one that is has not thoroughly explored through full examination.

Meanwhile, the Guidance presupposes that, after FDA notification, FDA will proceed to determine which of the tests are “high risk” and therefore require submission of an application for Pre-Market Approval. And FDA’s guidance for identifying “high risk” laboratory-developed testing services will not even be issued for two years. Thus, a meaningful economic impact analysis cannot be performed, and there is simply no basis on which FDA could conclude that its jurisdictional expansion will be cost-effective.

More broadly, the Guidance threatens to pose a serious obstacle to innovation and chill investment in medical testing advancements by disrupting the familiar regulatory landscape that has rationally governed clinical laboratories for decades. FDA’s approach is inconsistent at its core with the way new laboratory-developed testing services have developed, with rapid identification of genes and biomarkers, and with reliance on cutting-edge research that is not conducive to being frozen by the need for regulatory approvals. Laboratory tests are constantly evolving in response to rapid scientific advances. Given the threats of Ebola and other infectious diseases on the horizon, now is not the time to delay patient access to vital laboratory-developed testing services or to compromise America’s leadership in diagnostic discovery. FDA cannot impose radical transformations on matters of such great social and economic importance without conducting a full assessment of the broader impact.

In sum, FDA has taken a procedural shortcut to subject laboratory-developed testing services to a regulatory regime that it has no legal authority to require in the first place. That is simply not the way that FDA, or any other federal agency, should act.

CONCLUSION

FDA lacks legal authority to exercise jurisdiction over laboratory-developed testing services, and violates well-settled principles of administrative law in attempting to exercise such jurisdiction through guidance documents. The proposed Guidance should be withdrawn.