February 2, 2015

American Clinical Laboratory Association

Commissioner Margaret Hamburg, M.D.
Food and Drug Administration
Division of Dockets Management (HFA-305)
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

**RE: Framework for Regulatory Oversight of Laboratory Developed Tests; Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories; Availability (Docket No. FDA-2011-D-0360)**

**Food and Drug Administration Notification and Medical Device Reporting for Laboratory Developed Tests; Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories; Availability (Docket No. FDA-2011-D-0357)**

Dear Commissioner Hamburg,

Following are the comments of the American Clinical Laboratory Association ("ACLA") on the above-referenced Draft "Guidances" released by the Food and Drug Administration ("FDA" or the "Agency") on October 3, 2014.[1] ACLA is an association representing the nation's leading providers of clinical laboratory services, including local, regional, and national laboratories. Its diverse membership includes a broad array of clinical laboratories: large national independent labs, reference labs, esoteric labs, hospital labs, and nursing home labs. ACLA members are actively engaged in the development and performance of countless laboratory-developed testing services (LDTs) that have helped transform the standard of clinical care in this country and provide vital information to physicians caring for patients, and they are committed to providing accurate, reliable, and clinically meaningful diagnostic testing services for the benefit of patients.

## SUMMARY OF ACLA'S COMMENTS

FDA lacks the statutory authority to regulate laboratory-developed testing services. Congress has conferred upon FDA the authority to regulate medical devices, yet laboratory-developed testing services are not "medical devices." There are numerous indications that Congress has never intended for FDA to regulate laboratory-developed testing services, including: (i) the statutory definition of a "device," (ii) the statutory "commercial distribution" requirement, (iii) the detailed requirements Congress enacted in the Clinical Laboratory Improvement Amendments ("CLIA") specifically tailored to clinical laboratories and their tests, (iv) the nearly three decades of comprehensive regulation of clinical laboratories by the Centers for Medicare and Medicaid Services, (v) the legislative histories of both CLIA and the 1976 Medical Device Amendments, and (vi) Congress' specific directive that the FDA *not* regulate the practice of medicine.

[1] 79 Fed. Reg. 59776 (Oct. 3, 2014); 79 Fed. Reg. 59779 (Oct. 3, 2014).

Even if FDA had the statutory authority to regulate laboratory-developed testing services – which it does not -- it would have to do so through notice-and-comment rulemaking, rather than through its relatively informal guidance process. That is because FDA intends to impose novel binding obligations on the public and on the Agency itself; it does not purport merely to interpret existing obligations. The wholesale change that the Agency proposes would need to undergo a thorough vetting process that is not possible under its interpretive guidance framework. The Draft "Guidances" themselves include numerous conceptual flaws that underscore FDA's misguided attempt to fit a square peg – laboratory-developed tests – into the round hole of current medical device regulatory requirements. For these reasons, FDA must withdraw the Draft "Guidances."

## I. BACKGROUND ON LDTS

Laboratory-developed testing services are diagnostic tests that are developed, validated, and performed by highly-trained professionals within a single clinical laboratory entity. Physicians routinely depend on LDTs to assist in making crucial medical decisions about the best course of treatment for their patients. Laboratory-developed testing services are performed on blood, urine, tissue, or other types of specimens at the request of a physician. An LDT is a methodology or process – based on a laboratory's unique knowledge of testing 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.

Unlike a drug or device, which is a finished, packaged article of commerce accompanied by instructions for use by others, a laboratory-developed testing service is a proprietary method that only the developing laboratory entity can execute. That service 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 or distributed as a kit or an article of commerce, and the protocol is not transferred in any manner to other laboratories, hospitals, or facilities outside of the developing laboratory entity. No physical product is sold or distributed. No article of personal property is transferred such that title passes from one party to another.

Physicians routinely rely on laboratory-developed testing services, ranging from common 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 infectious diseases. While there are numerous ready-made *in vitro* diagnostic ("IVD") test kits available in the marketplace, in many instances, the scientific knowledge that forms the basis for the development of a test kit is outdated by the time the kit is approved by FDA, which oftentimes takes years. Further, there are many biomarkers and analytes for which no commercial standardized test kits yet exist. Where test kits would not generate the economies of scale necessary to justify development of a commercially marketed product, laboratory-developed testing services often are the only available options. 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, 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.

Laboratories that provide laboratory-developed testing services are subject to comprehensive regulation by the Centers for Medicare and Medicaid Services ("CMS"), state regulators, and in many instances the College of American Pathologists ("CAP"), which is the preeminent specialty society of pathologists and which accredits many labs. Laboratories regulated by CMS under the Clinical Laboratory Improvement Amendments ("CLIA")[2] and implementing regulations are required to be CMS-certified, and many are state-licensed as well. Those certifications and licensure requirements work to ensure that laboratories provide accurate information to physicians and that laboratory testing processes are supervised by qualified personnel. For example, CLIA requires a qualified medical director to oversee all high-complexity clinical tests, and it subjects an LDT to analytic validity requirements to ensure that it does, in fact, measure the analyte (*e.g.*, genotype, chemical, protein) it purports to identify. Furthermore, precisely because the tests are not required to undergo premarket FDA approval, laboratories are able to innovate and improve their services rapidly and continually. Under the existing regulatory oversight framework under CLIA, laboratories thus have the flexibility and technical expertise to adapt in real time to the latest scientific advances.

## II. FDA LACKS STATUTORY AUTHORITY TO REGULATE LABORATORY-DEVELOPED TESTING SERVICES.

The text of the Federal Food, Drug, and Cosmetic Act ("FDCA") and the broader statutory context foreclose FDA's attempt to expand its jurisdiction to encompass laboratory-developed testing services. Congress has 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. Further, 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 that are sold in interstate commerce, not the kinds of services performed by laboratories. Moreover, multiple canons of construction,

[2] 42 U.S.C. § 263a *et seq*.

discussed below, underscore that Congress did not grant FDA the enormous regulatory power it seeks to exercise without actually stating that it was doing so. FDA's attempted expansion of its authority is inconsistent with the statutory text and would raise serious constitutional questions that Congress itself sought to avoid.

### A. FDA Has Improperly Asserted Sweeping Authority Over LDTs.

Although laboratory-developed testing services long have been regulated both by CMS and by the states, 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, which were 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, and in a statute that is primarily focused on the distinct problems concerning mass-produced, mass-marketed, and mass-distributed drugs and devices moving in interstate commerce.[3]

FDA's so-called "Guidance" documents seek to impose substantial, 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 claims jurisdiction, the "Guidances" announce a risk-based, phased-in approach. The main elements of this new framework include numerous obligations that laboratories must observe in order to comply with numerous medical device regulations. These obligations include:

- Notification to FDA, or registration and listing, of laboratory-developed testing services (and "significantly" changed laboratory-developed testing services) under 21 C.F.R. Part 807, to classify them by risk levels and assist FDA in determining 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 death or serious injury;

- Premarket review of "high-risk" and "moderate-risk" laboratory-developed testing services to assess their clinical validity;

[3] 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 Compliance Policy Guide in 1992. After hearing numerous objections from stakeholders about the FDA's claim of regulatory authority over LDTs, in the final Compliance Policy Guide released in 1996, FDA stated that it believed it had authority to regulate laboratory-developed testing services but was not exercising that power as a matter of discretion.

- Compliance with Quality System Regulations, including the device-related design control procedures of 21 C.F.R. § 820.30(a)-(j); and

- Demonstration of the "clinical validity" of laboratory-developed testing services.

These requirements are not imposed uniformly 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 "Guidances" are finalized.

### B. FDA's Interpretation is Precluded by the Plain Text of the FDCA.

FDA's assertion of authority over laboratory-developed testing services is precluded by the plain text of the FDCA. Laboratory-developed testing services fall outside the realm of FDA's authority because they are not "devices" under 21 U.S.C. § 321(h) and they are not "introduc[ed] into interstate commerce for commercial distribution" under 21 U.S.C. § 360(k).

#### 1. Laboratory-Developed Testing Services Are Not "Devices."

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."[4] Under the FDCA, therefore, FDA has authority to regulate only manufacturers of commercially distributed medical "devices," including devices that 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.[5] Laboratory-developed testing services are not "devices." Such tests are proprietary methodologies, rather than physical products. Laboratories use 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 a "device" 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.[6] The words grouped in 21 U.S.C. § 321(h) are, without exception,

---

[4] 21 U.S.C. § 331(a).

[5] *See Oxford Dictionary of English* (3rd 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").

[6] 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,

physical articles that can move in interstate commerce. A traditional canon of construction dictates that words grouped in a list should be given related meaning.[7] Here, the statutory text itself reflects and reinforces that traditional canon by employing an inclusive catch-all term that uses the word "article." Laboratory-developed testing services are not physical "articles," much less articles moving in commerce, and are categorically different from the items Congress enumerated as "devices." Shoe-horning 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."[8]

Laboratory-developed testing services do not become medical devices 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. 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 could be deemed "devices" subject to the FDCA's regulations. For example, every time a radiologist reads an x-ray, 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.

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 IVD test kits that currently are regulated by FDA perform clinical testing functions that are similar to laboratory-developed testing services.[9] But IVD test kits are devices by any plausible reading of the statutory definition. Laboratory testing services, on the other hand, are not "devices" simply 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.

The statute's 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 an impermissible interpretation of it.

**2. Laboratory-Developed Testing Services are Not Introduced into Interstate Commerce.**

---

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).

[7] *Dole v. United Steelworkers of Am*., 494 U.S. 26, 36 (1990).

[8] *See Gutierrez v. Ada*, 528 U.S. 250, 255 (2000).

[9] *See* FDA Denial of ACLA Citizen Petition ("FDA Denial") at 4-5.

Section 510(k) of the FDCA, which applies FDA's premarket 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.[10]

FDA has defined "commercial distribution" to mean "any distribution of a device intended for human use which is held or offered for sale" and generally to require delivery to purchasers or consignees.[11]

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 the website."[12] Mere promotion, however, is not sufficient to establish commercial distribution. The legislative history of the Medical Device Amendments confirms this commonsense conclusion by noting specifically that "commercial distribution" does not include "mere announcements of intent to market a device."[13] The promotion of a service is different from the distribution of an article.

Further, a laboratory developed testing service is not held or offered for sale as a kit. A physician's test order for a laboratory developed testing service is satisfied by performing a service in-house and reporting to the ordering physician the result of that service, not by transferring title to and possession of the testing methodology or protocol to the ordering physician as a third party purchaser. Therefore, laboratory developed testing services do not satisfy the "commercial distribution" requirement of the FDCA.

### 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,

---

[10] 21 U.S.C. § 360(k).

[11] 21 C.F.R. § 807.3(b); FDA Manual of Compliance Policy Guide § 300.600 (1978, reissued 1987) ("CPG").

[12] FDA Denial at 13 (emphasis added).

[13] H.R. Rep. 94-853, at 36 (1976).

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."[14] In 1997, Congress added a provision making explicit what had always been implicit: that the FDCA does not regulate the practice of medicine.[15] The FDA's proposal would run afoul of that principle.

The laboratory is providing its proprietary testing services each time it performs laboratory-developed testing for a specific patient at the request of the ordering physician, who exercised his medical judgment to order the test within the context of a doctor-patient relationship. The physician applies independent judgment with respect to the test results obtained from the testing services in order to inform his diagnostic and treatment decisions for an individual patient based on medical judgment. This is the practice of medicine. The laboratories do not manufacture physical product. They provide a medical service, just as physicians do.

The fact that laboratory testing entails use of tangible articles does not change the fact that laboratory developed testing services do not fall within the device definition. Congress did not intend that FDA would regulate every clinical service as a medical device simply because the service involves the use of tangible articles which themselves may be subject to FDA regulation. Otherwise, every surgical procedure or physical examination that is performed on a patient using tangible devices would be subject to FDA regulation. Congress made clear in FDCA section 1006 that FDA has no authority to regulate the practice of medicine, which includes the practice of laboratory medicine.[16]

### C. Principles of Statutory Construction Preclude FDA's Jurisdiction over LDTs.

Congress is presumed not to address issues of great "economic and political significance" in a "cryptic … fashion."[17] The Supreme Court has said, "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."[18] Congress is presumed not to have dramatically upended a well-settled regulatory landscape without some clear indication in the relevant statutory text and history.[19] FDA's assertion of its authority to regulate

---

[14] *Linder v. United States*, 268 U.S. 5, 18 (1925).

[15] *See* 21 U.S.C. § 396.

[16] *Id.*

[17] *See FDA v. Brown & Williamson Tobacco Corp*., 529 U.S. 120, 160 (2000); *see also Whitman v. Am. Trucking Ass'ns*, 531 U.S. 457, 468 (2001) (Congress "does not, one might say, hide elephants in mouse holes").

[18] *Util. Air Regulatory Grp. v. E.P.A.*, 134 S. Ct. 2427, 2444 (2014).

[19] *See id.*; *Brown & Williamson*, 529 U.S. at 160; *cf. Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 362-63, 369-70 (2002) (concluding that traditional understandings were wrong would "not make sense" where, for "approximately the first 50 years after the enactment of the FDCA ... [p]harmacists continued to provide patients with compounded drugs without applying for FDA approval").

thousands of laboratories already subject to regulation by CMS and state regulators "falls comfortably within the class of authorizations that [the Supreme Court has] been reluctant to read into" statute in the absence of unambiguous text.[20]

Additionally, the "rule of lenity" requires that when a statute carries criminal penalties, "less constrained" constructions must be rejected absent "Congress' clear instruction otherwise."[21] 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.[22] That tenet applies to the FDCA, which provides for both civil and criminal penalties for violations and must be interpreted consistently in both contexts. FDA's theory would mean that the innumerable laboratories that have openly bypassed FDA's device regulations over the past four decades 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."[23] Any construction of the FDCA that would render thousands of CMS- and state-regulated laboratories a class of violators of federal criminal law rests on a highly implausible interpretation of what Congress did and what it intended.

### 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. Nonetheless, the broader context of the statutory scheme as a whole makes clear what already is evident from the face of the FDCA: Congress' enactment of CLIA's 1988 amendments leaves no doubt that FDA does not have the authority to regulate LDTs. 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).

Many, but not all, laboratories already were regulated before enactment of the Clinical Laboratory Improvement Amendments of 1988 and the 1976 Medical Device Amendments. Congress passed the original Clinical Laboratory Improvement Act in 1967. Physician office labs and certain other labs were not covered by the 1967 legislation, but most laboratories that were accepting specimens were covered. Laboratories already had been regulated for almost a decade when Congress passed the Medical Device Amendments in 1976, yet Congress did not mention LDTs at all.

---

[20] *Util. Air Regulatory Grp.*, 134 S. Ct. at 2444.

[21] *Skilling v. United States*, 561 U.S. 358, 411 (2010).

[22] *United States v. Lanier*, 520 U.S. 259, 266 (1997).

[23] *Id.* (quoting *Yi v. Sterling Coll. Ctrs.*, 480 F.3d 505, 510-511).

In the CLIA 1988 amendments, passed 12 years after the 1976 Medical Device Amendments, Congress created a detailed statutory framework specifically to govern clinical laboratories and their tests. 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."[24] CLIA prohibits laboratories from soliciting or accepting specimens for laboratory tests until the laboratories are CMS-certified.[25] 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." CLIA also requires laboratories to participate in regular "proficiency testing."[26] The enactment of the CLIA amendments in 1988 would be inexplicable if Congress had intended in the 1976 Medical Device Amendments, as FDA asserts, to subject laboratory-developed testing services to the FDCA's device regulations.

Neither CLIA's statutory text nor its 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. Making the absence of FDA references all the more notable, 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."[27] Accordingly, the legislative history is replete with references to the overlapping standards of CLIA, of the Medicare statute, and of state regulation, but it is 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 it included a section entitled "Current Regulatory System" that contained no mention of FDA.[28] 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 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[29]—a provision that, on FDA's

---

[24] 42 U.S.C. § 263a(a).

[25] 42 U.S.C. § 263a(b).

[26] 42 U.S.C. § 263a(f)(1).

[27] 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.").

[28] H.R. Rep. No. 100-899, at 11-12 (1988) (emphasis added).

[29] 42 U.S.C. § 263a(g)

reading, would be rendered superfluous by the FDCA's requirement that device establishments submit to inspections.

Worse still, CMS regulations would conflict with the FDA "Guidances." 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."[30] Any FDA guidance requiring this latter category to undergo premarket device approval processes thus would be irreconcilable with the prescriptions in 42 C.F.R. § 493.1253(b)(2). Similarly, CMS regulations allow laboratories to update their tests continually to reflect new scientific developments as long as they appropriately validate and document any modifications. But FDA's "Guidances" would, in sharp contrast, require supplemental filings and FDA authorizations for any modifications. This would be an impractical mandate, given the constantly evolving and dynamic nature of laboratory-developed testing services.

## III. EVEN IF FDA HAD STATUTORY AUTHORITY TO REGULATE LDTS, IT MAY NOT DO SO THROUGH GUIDANCE DOCUMENTS, RATHER THAN THROUGH NOTICE-AND-COMMENT RULEMAKING.

Even if FDA had the authority to regulate LDTs, it could not do so without complying with notice-and-comment rulemaking procedures. 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 to enlarge its control over laboratory-developed testing services through mere informal "Guidance" documents.

### A. FDA's "Guidances" Would Impose Binding, Substantive Obligations on Private Parties.

FDA has issued so-called "Guidance" documents that would go well beyond providing helpful guidance. Instead, they would seek to impose significant, binding requirements on private parties that provide laboratory-developed testing services. The draft "Guidances" propose a risk-based, phased-in approach to regulatory oversight of laboratory-developed tests. The main elements of the framework include numerous obligations that laboratories would be required to observe in order to comply with numerous medical device regulations. These obligations would include notification to FDA, or registration and listing, of laboratory-developed testing services (and "significantly" changed laboratory-developed testing services) under 21 C.F.R. Part 807, to classify them by risk levels and assist FDA in determining what premarket review requirements to enforce against which tests; reporting of "adverse events" under 21 C.F.R. § 803.50; premarket review of "high-risk" and "moderate-risk" laboratory-developed testing services to assess their analytical validity and validity; compliance with Quality System Regulations, including 21 C.F.R.

[30] 42 C.F.R. § 493.1253(b)(2).

§ 820.30(a)-(j); and demonstration of the "clinical validity" of laboratory-developed testing services.

FDA's effort to impose these requirements 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 ("APA"), 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.[31] Here, for several reasons, FDA's "Guidances" announce substantive rules that are subject to notice and comment.

To begin with, FDA's "Guidances" have the purpose and effect that characterize a substantive legal rule: they purport to impose legally binding obligations or prohibitions on regulated parties and form the basis for enforcement actions.[32] By contrast, an interpretive rule merely interprets a prior statute or regulation and does not purport to impose new obligations or prohibitions or requirements. FDA's pronouncements thus plainly amount to "lawmaking," the hallmark of a substantive rule.

For the same reasons, FDA's "Guidances" cannot be viewed merely as "general statements of policy" that "explain how the agency…will exercise its broad enforcement discretion or permit discretion under some extant statute or rule."[33] 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."[34] It imposes no obligations or prohibitions on regulated entities such that they may ignore the guidance without suffering any legal penalties or disabilities. Here, FDA's "Guidances" impose new binding "norms" with no real basis in the statute. For example, laboratories now would be obligated to notify FDA of each laboratory-developed test that they have developed and to provide basic information within six months of the finalization of the draft "Guidances" – a new concept that does not apply to any devices currently. Laboratories would be obligated to comply with FDA's risk classification and seek premarket approval of "high risk" tests. And there is no question that FDA would bring enforcement actions and penalties against laboratories if they did not comply.

---

[31] *See* 5 U.S.C. § 553. 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).

[32] 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, v. McCarthy,* 758 F.3d 243, 251 (D.C. Cir. 2014). Thus, an interpretive rule involves no "lawmaking" or "change in the legal norm." *Syncor Int'l Corp. v. Shalala*, 127 F.3d 90, 94 (1997).

[33] *Nat'l Min. Ass'n at* 252.

[34] *Syncor* at 94.

Although FDA has claimed that by issuing its "Guidances" it is doing no more than announcing a revised enforcement policy regarding laboratory-developed testing services,[35] the "label an agency attaches to its action is not determinative."[36] Here, the substance of FDA's actions – imposing a host of new mandatory obligations on laboratories that offer laboratory-developed testing services – makes clear that the agency has gone well beyond simply stating its non-binding views about proper enforcement policy.

FDA's foray into impermissible lawmaking is demonstrated further by the fact that its "Guidances" 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 those "whose 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*," need not comply with the FDCA's device-registration requirements.[37] Moreover, the regulations explicitly set forth the reason that clinical laboratories (including those engaged in laboratory-developed testing services) are exempted from registration: "such registration is not necessary for the protection of the public health."[38]

FDA's about-face upends nearly four decades of established practice. While an agency is not prohibited from changing its position, notice-and-comment rulemaking is a critical safeguard against the risk of unfair surprise for regulated parties. 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.[39]

### B. FDA May Not Circumvent the Requirements of Rulemaking by Issuing "Guidance" Documents Instead.

FDA may not use an informal guidance process to avoid the vital protections guaranteed for nearly seven decades by the APA. FDA has an obligation to consider and to respond meaningfully to comments and undertake economic analysis of the regulatory impact of its proposed action.

---

[35] *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").

[36] *Continental Airlines, Inc. v. CAB*, 522 F.2d 107, 124 (D.C. Cir. 1974); *see also Appalachian Power Co.*, 208 F.3d 1015, 1024 (D.C. Cir. 2000) ("an agency may not escape the notice and comment requirements...by labeling a major substantive legal addition to a rule a mere interpretation").

[37] 21 C.F.R. § 807.65(i) (emphasis added).

[38] 21 C.F.R. § 807.65.

[39] *See Syncor*, 127 F.3d at 95.

### 1. FDA May Not Issue "Guidance" Documents to Evade the APA's Notice-and-Comment Requirements.

Section 553(c) of the Administrative Procedure Act requires an agency to consider the comments submitted to it. The requirement to consider public comment is no mere formality. Rather, it is designed to ensure that an agency considers all sides of an issue and makes informed decisions when finalizing rules that will bind the agency and the public. Closely related to the requirement that the agency consider comments is the rule that it meaningfully respond to relevant and significant ones.

FDA's "Guidances" bypass the APA's well-established notice-and-comment procedures. Instead, they were issued consistent with FDA's so-called "good guidance practices" regulation. Although FDA is accepting public comments on the guidance documents, there is a key difference between "good guidance practices" and APA rulemakings: the FDA's guidance policy provides merely that FDA will review comments received and prepare a final version that "incorporates suggested changes, when appropriate." FDA thus is left to decide on its own what is "appropriate," and it is not required to respond to significant comments. 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."[40] That is all FDA offers here.

### 2. FDA May Not Issue "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.[41] However, FDA has not considered the cost and economic impact of its proposed extension of FDA jurisdiction over clinical laboratories.

The absence of an economic impact analysis is a particularly glaring omission given the sweeping practical effects of FDA's proposed policy change. FDA's assertion of jurisdiction would burden clinical laboratories significantly, superimposing a duplicative bureaucratic regime on a vibrant and constantly evolving laboratory testing industry that already is regulated under CLIA. 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 should be resolved through a thorough review of all comments and responses to each.

Economic impact analysis is essential where FDA's new regulatory responsibilities would be daunting for the Agency. There are an estimated 11,000 laboratories currently permitted to use and develop laboratory-developed testing services. Under the "Guidances," every laboratory developing and performing LDTs would be required to "notify" FDA that it is performing a laboratory-developed test and provide extensive information about each laboratory-developed test

---

[40] *McLouth Steel Products Corp. v. Thomas*, 838 F.2d 1317, 1323 (D.C. Cir. 1988).

[41] *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).

being offered by that laboratory within six months of the issuance of the final guidance. 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.

More broadly, the "Guidances" threaten to pose a serious obstacle to innovation and chill investment in medical testing advancements by disrupting the familiar regulatory landscape that has 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 regulatory approvals. Laboratory tests evolve constantly in response to rapid scientific advances. FDA cannot impose radical transformations on matters of such great social and economic importance without conducting a full assessment of the broader impact. Such assessment is available to the public only through notice-and-comment rulemaking.

## IV. THE DRAFT GUIDANCES ARE CONCEPTUALLY FLAWED.

In addition to issues addressed above, ACLA members have identified many conceptual flaws in FDA's Draft Guidances. These issues demonstrate the impossibility of trying to fit the square peg of LDTs into the round hole of existing medical device regulations, and they underscore the statutory conclusion that laboratory-developed testing services simply do not qualify as medical "devices."

- Clinical laboratories would be subject to duplicative and sometimes conflicting regulation by CMS and the FDA in areas such as inspection and quality control. Initially, FDA stated that it planned to issue a third guidance document, which would clarify how to harmonize any conflict between CLIA and FDA regulations. More recently, FDA has indicated that it intends to leave such guidance to a third-party organization. By failing to provide such guidance and leaving it to a third party group, FDA implicitly acknowledges the difficulty that laboratories will face, and it is shirking its responsibilities in this area. Further, even if FDA were to issue its own explanation of how laboratories should navigate compliance with both FDA and CLIA regulations, laboratories would still face potential exposure to conflicting obligations and liabilities without publication of a consistent interpretive and enforcement approach by CMS.

- The "Guidances" refer repeatedly to "laboratories that manufacture LDTs." Yet LDTs are services; they are not manufactured articles.

- FDA proposes to define "LDT" as an IVD intended for clinical use and designed, manufactured and used within a facility with a single CLIA certificate. FDA uses this narrow definition as a criterion for applying the "traditional LDT" and "LDT for unmet needs" categories for continued enforcement discretion for certain requirements. However, FDA states that it otherwise intends to apply the risk-based framework to any test marketed as an LDT by a laboratory, regardless of whether it meets FDA's definition of an LDT, in recognition of the fact that many laboratories define LDT much

more broadly and that applying the narrower definition could result in interruption of patient access to vital testing, which FDA says it wishes to avoid. But the use of the narrow LDT definition in the "traditional LDT" and "LDT for unmet needs" categories threatens the very patient access to testing that FDA says it wishes to avoid. Further, where an entity that owns several clinical laboratories develops a test in one of its labs and then performs the same test, using the same methodology on the same instruments in several of the labs in its network, to treat each facility's test as a unique LDT in applying the Framework would result in unnecessarily duplicative and expensive regulation of the same test, wasting resources for both laboratories and the FDA.

- Other than three narrow enumerated categories of LDTs, the FDA does not intend to say what it considers to be a "high risk" or "moderate risk" LDT until long after finalizing its regulatory scheme, and would be basing these as-yet undetermined risk classifications upon recommendations of as-yet unidentified panels of consultants. Ready classification of any risks associated with LDTs has eluded stakeholders and the agency for years, and it is unrealistic for FDA to assume it can assign such classifications easily. Moreover, it will be difficult for laboratories to operate and attract necessary investments if they are uncertain for years if, when, and how they may be regulated by FDA, and what requirements a laboratory would need to meet in order to make submissions to the FDA under the proposed "Guidances" (e.g., submissions for a PMA must be under QSR development at time of submission which could be as short as 12 months after the "Guidances" are finalized).

- It is unclear how the FDCA concept of "labeling" could or should apply to a laboratory-developed testing service, since the service is not a tangible item and it is not performed or offered outside of the developing laboratory entity. There is no packaging to which a label would be affixed, and there is no package insert with information and instructions for others.

- It is not clear what would be considered an "adverse event" or a "device malfunction" in the context of LDTs. Would FDA consider it an "adverse event" if a patient's cancer returned after an LDT predicted a 90 percent chance that it would not? Would it be a "malfunction" if a momentary interruption in result reporting were to occur due to information system problems, but the problem was resolved without significantly delaying result delivery? Under the User Facility regulations, clinical laboratories are already under the obligation to report adverse events to the manufacturers of reagents and instruments used in the laboratory, so it is unclear exactly what laboratories would be required to report outside of the existing User Facility requirements. Moreover, how would FDA separate technical and medical process from their concept of a device, especially where technical preparation of specimens occurs outside of the control of the lab, for example, from a hospital source or where transportation of specimens may affect a lab result?

- If laboratories performing LDTs are subject to Medical Device Reporting ("MDR") requirements as "manufacturers," would the physicians who order LDTs and their

respective hospitals, ambulatory surgical facilities, nursing homes, outpatient treatment facilities, or other facilities in which the physicians may order LDTs, be subsequently subject to MDR requirements as "user facilities" with respect to LDTs? If so, there are hundreds of thousands of physicians in the U.S. who are likely unaware of this new potential obligation, particularly due to the fact that, unlike medical devices they have purchased and used in their offices every day (*e.g.*, x-ray machines or test kits), they do not own the LDT, they have not operated it to produce a result, and it occupies no space in their offices.

- FDA does not address whether anatomic pathology services would be considered LDTs subject to the regulatory regime; the wording of the draft "Guidances" is imprecise enough to possibly encompass anatomic pathology services. A pathologist is practicing medicine in his or her field of expertise, in the same way as any other physician practices medicine, which is markedly outside of the FDA's jurisdiction to regulate.

- FDA does not address whether a laboratory consultation (when a laboratory's clinical consultant, a position required by CLIA, speaks with an ordering physician about the uses of a test) could be considered "off-label promotion" of a test.

- Some provisions, such as Quality System Regulation ("QSR") requirements, would not be enforced until a PMA is submitted or a 510(k) clearance order is issued; but as a practical matter, laboratories would have to implement QSR programs well in advance of submission of a PMA to ensure its approval, and it would take years for most laboratories to implement such programs. Since PMAs for certain high risk LDTs would be required within 12 months of the final guidance to avoid enforcement activity, implementation of QSR programs would need to begin before finalization of the guidance; however, laboratories are unlikely to be willing to incur the cost of QSR programs before finalization of the guidance is certain. FDA's QSR requirements, such as design controls, usually are imposed on manufacturers who are in the process of developing new products. However, most laboratories have been offering their LDTs for decades, if not longer, so it will be impossible for them to go back and re-create design files that they were never required to have in the first place.

- Generally, when a laboratory modifies an FDA-approved or cleared test kit, that new test is considered an LDT. Indeed, the CLIA regulations specifically address and authorize this laboratory practice. Laboratories make such modifications routinely, usually because they have determined more efficient ways to run a test or because they have determined some other ways to use a kit, such as with a different type of specimen or with other variations not encompassed in the manufacturer's instructions (such as instrumentation models that may differ from those discussed in the manufacturer's labeling). FDA appears to intend to treat most if not all of these modifications as new LDTs that would be subject to risk-based premarket review, which would tax FDA's limited resources, freeze out future test improvements and even curtail laboratories from purchasing new analytical instruments because such a purchase may require them to do a new submission to the FDA.

- FDA has committed to refraining from imposing user fees on laboratories or LDTs during the MDUFA III period, but FDA's fee waiver authority is limited to 2% of user fee revenue annually (the equivalent of user fees for approximately 10 PMAs annually) and the draft guidance imposes no limits on the number of PMAs that may be required for LDTs. How would FDA keep its commitment?

## V. CONCLUSION

In summary, FDA must withdraw the Draft "Guidances" in their entirety. The Agency lacks the statutory authority to regulate laboratory-developed testing services. If it did have such authority, it would need to issue its proposals through notice-and-comment rulemaking. Thank you for your consideration of ACLA's comments.

Sincerely,

Alan Mertz, President
American Clinical Laboratory Association