DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
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JUL 31 2014

Alan Mertz
American Clinical Laboratory Association
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Washington, DC 20005

Re: Docket No. FDA-2013-P-0667

Dear Mr. Mertz:

The Food and Drug Administration (FDA, the agency) has reviewed the citizen petition that the American Clinical Laboratory Association (ACLA) submitted on June 4, 2013, pursuant to 21 CFR 10.30. In the petition, ACLA requests that FDA "(1) refrain from issuing draft or final guidance or a proposed or final rule purporting to regulate LDTs [laboratory-developed tests] as devices under the FDCA; and (2) confirm in response to [the] citizen petition that LDTs are not devices under the FDCA."

FDA has reviewed ACLA's petition, as well as the comments on the petition and other information available to the agency, and for the reasons explained below, is denying the petition.[1]

I. Background

In 1976, Congress enacted the Medical Device Amendments (MDA), which amended the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) to create a comprehensive system for the regulation of medical devices intended for use in humans. At that time, the definition of a device was amended by adding to the existing definition the terms "implement, machine . . . implant, *in vitro reagent*, or other similar or related article . . . ." 21 U.S.C. § 321(h) (emphasis added). While the definition of device clearly includes all *in vitro*[2] diagnostic devices (IVDs) intended for use in clinical diagnosis/treatment, FDA has generally exercised enforcement discretion so that the agency has generally not enforced applicable provisions under the FDCA and FDA regulations with respect to laboratory-developed tests (LDTs).[3]

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[1] FDA is also responding to two other citizen petitions regarding laboratory-developed tests (LDTs) submitted by the Washington Legal Foundation (Docket No. FDA-2006-P-0143) and Genentech, Inc. (Docket No. FDA-2008-P-0638). FDA's response to these petitions is available at www.regulations.gov (search by docket number).

[2] *In vitro* means outside the living body and in an artificial environment. *See* Merriam-Webster's Collegiate Dictionary (11th ed. 2004).

[3] FDA defines the term laboratory-developed test as an IVD that is intended for clinical use and designed, manufactured and used within a single laboratory, i.e., a facility with a single CLIA (Clinical Laboratory Improvement Amendments of 1988) certificate.

Initially, laboratories manufactured LDTs to serve the needs of the local patient population. These LDTs, which were generally manufactured with legally marketed components (i.e., general purpose reagents, immunohistochemical stains, and other components marketed in compliance with FDA regulatory requirements), were relatively simple, well-understood tests or tests used to diagnose rare diseases, and were intended to be used by physicians and pathologists within a single institution in which both types of healthcare professionals were actively part of patient care.[4]

Today, LDTs often use components that are not legally marketed, and rely more heavily on complex instrumentation and software to generate results and clinical interpretations. In addition, LDTs are often used to assess common diseases and conditions, including those that are serious and life-threatening, and to inform critical treatment decisions, and are often performed in laboratories outside of the patient's health care setting. An increasing number of LDT manufacturers are corporations that offer a limited number of complex, high-risk devices nationally as opposed to being hospitals or public health laboratories that use a wide range of devices designed specifically to meet the needs of their local patients. In addition, even when FDA approved/cleared tests are available for a disease or condition, laboratories often continue to manufacture and offer LDTs for those same diseases or conditions that have not been reviewed by the agency.

These attributes of modern LDTs may increase risk for patients, in the absence of appropriate FDA oversight. Indeed, modern LDTs have risk profiles similar to IVDs offered by other device manufacturers because similar to other IVDs, LDTs often incorporate complex technology, are often widely offered for common diseases and conditions, and are increasingly used in guiding critical clinical management decisions. Consequently, FDA announced its intent to reconsider its policy of enforcement discretion over LDTs. *See* 75 FR 34463 (June 17, 2010). FDA held a public meeting to discuss issues and stakeholder concerns regarding LDT oversight. The agency also provided additional opportunity for comment through a public docket. *See id.* Since then, the agency has considered the comments received and has been developing an enforcement policy for LDTs that takes into consideration assuring that LDTs are safe and effective while recognizing the importance of fostering innovation. After providing the 60-day prior notice to Congress required under section 1143 of the Food and Drug Administration Safety and Innovation Act (FDASIA), Pub. L. 112-144, 126 Stat. 1130, FDA plans to publish its proposed enforcement policy for LDTs in a draft guidance document. The public will have an opportunity to comment in accordance with good guidance practices. 21 CFR 10.115. While this policy is being considered, as is true for any product under its jurisdiction, FDA may take any enforcement action under the Act that it deems necessary to protect the public health.

II. Statutory and Regulatory Authorities

Under section 201(h) of the FDCA, a device is defined as "an instrument, apparatus, implement, machine, contrivance, implant, *in vitro reagent*, or other similar or related article, including any component, part, or accessory, which is (1) recognized in the official National Formulary, or the

[4] Many of these LDTs were likely preamendment devices, i.e., devices that were on the market before May 28, 1976, the date of enactment of the MDA.

United States Pharmacopeia, or any supplement to them, (2) 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 (3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes." 21 U.S.C. § 321(h) (emphasis added).

Additionally, FDA regulations define "*in vitro* diagnostic products" as "those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. These products are devices as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (the act), and may also be biological products subject to section 351 of the Public Health Service Act." 21 CFR 809.3(a).

Devices are subject to a comprehensive set of regulatory authorities under the FDCA called general controls that are applicable to all classes of devices unless specifically exempt. General controls include, but are not limited to, provisions that relate to establishment registration and device listing; premarket notification; prohibitions against adulteration and misbranding; recordkeeping and reporting, including adverse event reporting; and good manufacturing practice. 21 U.S.C. § 360c(a)(1)(A). Class II devices are also subject to special controls and class III devices are subject to premarket approval. *Id.* at § 360c(a)(1)(B) & (a)(1)(C). FDA regulation under these provisions ensures that devices are subject to the necessary controls to provide a reasonable assurance of safety and effectiveness. *Id.*

III. Discussion

ACLA argues that: (1) "FDA has no jurisdiction to regulate LDTs under the FDCA"; (2) "FDA regulation of LDTs would be contrary to the public health"; (3) "FDA regulation of LDTs as devices would result in numerous unintended consequences with significant economic repercussions for the United States laboratory industry"; and (4) to the extent stakeholders have concerns about possible gaps in the clinical validation of LDTs, "the most logical and appropriate solution would be to amend CLIA [Clinical Laboratory Improvement Amendments of 1988] and/or its regulations." Pet. at 2-3.

1. FDA has jurisdiction to regulate LDTs under the FDCA

A. LDTs are "devices" as defined in the FDCA

ACLA claims: "LDTs are not 'devices' as defined in the Act . . . LDTs are proprietary procedures for performing a diagnostic test using reagents and laboratory equipment. They are essentially know-how, not articles." Pet. at 2. We disagree. LDTs are devices within the plain language of the definition. Similar to IVD test kits manufactured by other device manufacturers, LDTs are test systems that consist of, among other things, instruments, *in vitro* reagents, and/or

other similar or related articles, either produced within the laboratory or purchased from other device manufacturers, that are intended for use in the "diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease." 21 U.S.C. § 321(h).[5]

Further, LDTs are "*in vitro* diagnostic products" within the meaning of the definition in FDA's regulations, i.e., "reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae." 21 CFR 809.3(a). As provided in the definition, *in vitro* diagnostic products are "intended for use in the collection, preparation, and examination of specimens taken from the human body" and "are devices as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (the act), and may also be biological products subject to section 351 of the Public Health Service Act." *Id.*

ACLA's discussion of LDTs that were developed prior to the availability of an FDA cleared/approved test underscores that LDTs are devices just as other IVDs developed by other manufacturers. For example, ACLA notes that "laboratories developed and validated an LDT version of the Western blot to meet the acute need to establish definitive diagnosis of HIV-1. The FDA approved HIV-1 Western blot did not become available for another two years." Pet. at 14-15. Further, some stakeholders have noted that some laboratories are manufacturing and offering LDTs even when FDA cleared/approved tests are available. *See, e.g.,* Citizen Petition from Genentech, Inc. (Dec. 5, 2008) at 7-8 (noting that some clinical laboratories offer their own HER-2 tests using new technology for the purpose of selecting patients for Herceptin® (trastuzumab) therapy, even though FDA approved HER-2 tests are available), Docket No. FDA-2008-P-0638. In a comment submitted to the citizen petition docket, the Combination Products Coalition, an association of drug, biologic, and device manufacturers, pointed out that both "labs and non-labs offer products with similar technologies, and similar uses that can help or harm patients." Combination Products Coalition, Comment to Docket No. FDA-2013-P-0667 (Combination Products Coalition Comment), at 18.

ACLA does not dispute that FDA has jurisdiction over other IVDs that otherwise meet the FDCA's device definition but are not manufactured by laboratories. ACLA acknowledges that IVD test kits sold to laboratories by other device manufacturers are "products containing all or most of the components needed to perform a test, such as reagents and equipment." Pet. at 1. LDTs include the same types of articles that other device manufacturers may include in their test kits, and the procedures developed by a laboratory for performing its LDT are functionally equivalent to the instructions for use that other device manufacturers provide with their test kits

[5] Courts have generally upheld FDA's broad interpretation of "device." *See, e.g., United States v. 22 Rectangular or cylindrical finished devices, "The STER-O-LIZER MD-200,"* 714 F. Supp. 1159, 1165 (D. Utah 1989) (upholding FDA's determination that a sterilizing instrument is a device, although it does not come into direct contact with patients). A similar issue arose in *United States v. Article of Drug . . . Bacto-Unidisk*, 394 U.S. 784, 793 (1969), in which FDA determined that an antibiotic screening test was a "drug" and subject to premarket review at a time when devices were not subject to those requirements. The manufacturer argued that the FDCA was not intended to cover articles used so indirectly for patient care. The Court rejected this argument: "Viewing the structure, the legislative history, and the remedial nature of the Act, we think it plain that Congress intended to define 'drug' far more broadly than does the medical profession." *Id.*

to instruct laboratories and other users on how to perform the test. Simply put, LDTs are essentially the same with respect to form and use as other IVDs regulated by FDA. The difference is that an LDT is developed and manufactured by a laboratory, whereas a non-LDT IVD kit is developed and manufactured by a device manufacturer that is not a laboratory.

There is nothing in the FDCA statutory language or the MDA legislative history to indicate that when two IVDs are the same but one is not an LDT and the other is an LDT, only the former is a device within FDA's jurisdiction. Rather, the statute reaches broadly to all IVDs that meet the device definition in 21 U.S.C. § 321(h), regardless of origin of manufacturing. When Congress amended the device definition in 1976 to explicitly include IVDs, it could have included such a limitation, but it chose not to do so. In adding IVDs to the device definition, Congress explicitly placed all IVDs within FDA's jurisdiction, without specifying or limiting their location of manufacture.[6]

B. Laboratories that manufacture and offer LDTs do not fall within the practice of medicine exception

ACLA further claims that "FDA has no authority to regulate the practice of medicine, which includes the practice of laboratory medicine." Pet. at 9. ACLA asserts that if FDA were to regulate LDTs, "every surgical procedure or physical examination that is performed on a patient using tangible devices would be subject to FDA regulation." *Id.* Although FDA generally does not regulate the practice of medicine, laboratories that manufacture and offer LDTs do not fall within the practice of medicine exception in section 1006 of the FDCA, which states: "Nothing in this Act 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 conditions or disease within a legitimate health care practitioner-patient relationship." 21 U.S.C. 396 (emphasis added).

Even assuming that health care practitioners in the laboratory are prescribing or administering LDTs, they are generally not prescribing or administering a *legally marketed device*. *Cf. United States v. Regenerative Sciences*, 878 F. Supp. 2d 248, 261 (D.D.C. 2012) (in concluding that the company's practice of medicine argument was unavailing, the court explained, "There is a difference between a licensed physician's use of an FDA approved drug such as doxycycline in an off-label way, which is permissible within the 'practice of medicine,' and adding doxycycline to a cell product to be administered to patients, which renders the latter a 'drug' that has connections to interstate commerce."), *aff'd* 741 F.3d 1314, 1320 (D.C. Cir. 2014) (stating that appellants' practice of medicine argument "would allow states to gut the FDCA's regulation of doctors, and thereby create an enormous gap in the FDCA's coverage" contrary to Congress's intent). Therefore, while the practice of medicine exception permits physicians to prescribe or

[6] ACLA asserts that any FDA assertion over LDTs would be "unjustified" because Congress did not mention LDTs when enacting the MDA, citing *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 160 (2000). Pet. at 9. In that case, however, FDA had previously denied that it had jurisdiction to regulate tobacco products. 529 U.S. at 125. Here, FDA has consistently taken the view that it has jurisdiction over LDTs. Further, LDTs are a subset of IVDs, many of which ACLA acknowledges are subject to FDA regulation. *See* Pet. at 14-15.

administer a legally marketed drug or device to their patients for any use they consider appropriate in the exercise of their medical judgment, the exception does not permit them to manufacture and offer unapproved drugs or devices. Most LDTs that are manufactured and offered by laboratories are unapproved devices in that they have not received premarket clearance/approval as required under the FDCA, and therefore fall outside of the practice of medicine exception.[7]

C. FDA and the Centers for Medicare and Medicaid Services (CMS) have concurrent, complementary jurisdiction over laboratories that manufacture LDTs

ACLA also asserts that "FDA regulation of LDTs as devices would be inconsistent with the detailed CLIA scheme and Congress' intent in fashioning it." Pet. at 9. To the contrary, the history of these statutes supports FDA's jurisdiction. FDA asserted jurisdiction over *in vitro* diagnostic products under the FDCA even before it obtained explicit jurisdiction over these products with the MDA in 1976. *See* 38 FR 7096, 7098 (Mar. 15, 1973). When Congress enacted the Clinical Laboratory Improvement Amendments of 1988 (CLIA or 1988 Amendments), it amended the existing Clinical Laboratory Improvement Act of 1967, which had previously established a licensing requirement for most laboratories operating in interstate commerce. Pub. L. No. 90-174. The original licensing requirement thus predated enactment of the MDA. The 1988 Amendments made this laboratory regulatory scheme more comprehensive by eliminating an interstate commerce requirement and certain exemptions, among other changes. Congress knew that laboratories were already regulated under the 1967 Clinical Laboratory Improvement Act when it amended the device definition in 1976 to clarify that IVDs were within FDA's jurisdiction. Had Congress believed that IVDs manufactured by laboratories were already regulated under the 1967 Clinical Laboratory Improvement Act, it could have excluded them when it amended the FDCA device definition. Instead, Congress added IVDs, without limitation, to the FDCA device definition.

Similarly, when Congress enacted the 1988 Amendments, it did not include language indicating that it intended to shift authority over laboratory-developed IVDs from FDA to the Health Care Financing Administration (HCFA).[8] Because there is no explicit statutory shift of authority over laboratory-developed IVDs from FDA to HCFA, congressional intent to effect such a change would have to be inferred. Such "repeals by implication are highly disfavored" and "will not be found unless an intent to repeal is 'clear and manifest.'" *Ruckelshaus v. Monsanto Co.*, 467 U.S. 986, 1017 (1984) (citations omitted); *Rodriguez v. United States*, 480 U.S. 522, 524 (1987) (citations omitted). As a result, "where two statutes are 'capable of co-existence, it is the duty of the courts, absent a clearly expressed congressional intention to the contrary, to regard each as effective.'" *Ruckelshaus*, 467 U.S. at 1018 (citations omitted). Indeed, in *Clinical Reference*

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[7] Although outside of the practice of medicine exception and subject to applicable requirements under the FDCA, including the requirement for premarket clearance/approval, as mentioned in Section I above, FDA has generally exercised enforcement discretion so that the agency has generally not enforced applicable premarket clearance/approval and other requirements under the FDCA and FDA regulations with respect to LDTs.

[8] CMS was known as the Health Care Financing Administration (HCFA) at the time CLIA and most of its implementing regulations were enacted. References to CMS in this document include HCFA.

Lab., Inc.[CRL] v. Sullivan, 791 F. Supp. 1499, 1509 (D. Kans. 1992), *aff'd in part, rev'd in part on other grounds*, *United States v. Undetermined Number of Unlabeled Cases*, 21 F.3d 1026 (10th Cir. 1994), the court found that "the FDCA and CLIA are not inconsistent," "that Congress intended to leave some regulatory overlap between the FDCA and CLIA," and "CLIA does not preempt the FDA's authority to regulate facilities like CRL," a clinical laboratory.

Moreover, the history of CLIA further illuminates Congress' intent to regulate a different area than is regulated by FDA under the FDCA and to achieve a different purpose. CLIA's enactment was prompted in large part by Congress' concern with the low quality of cytology services associated with Pap testing for cervical cancer. In particular, Congress noted the following:

> When specimens are collected, prepared, and analyzed correctly, the pap smear test is a highly effective diagnostic tool for the early detection of cervical cancer, which accounts for the loss of an estimated 7,000 lives every year. However, the Committee received disturbing testimony indicating that far too many of these fatalities are attributable to pap smear results which fail to indicate the presence of pre-cancerous or cancerous condition. In too many instances, such errors are the result of overworked and undersupervised cytotechnologists charged with the crucial responsibility of examining and categorizing cervical slides.

S. Rep. No. 100-561, at 26-27 (1988). This concern led Congress to conclude that "lack of quality assurance and quality control in the medical testing industry is pervasive." *Id.* at 20. These statements and the issue that gave rise to them indicate that Congress' concern was not with the quality of the tests themselves but with the quality of the human element in the provision of testing services, i.e., whether laboratory personnel were performing their jobs in a setting and in a manner that ensured accurate test results. Congress reaffirmed this intent in 1997 when it noted that "[t]he purpose of CLIA quality control, proficiency testing, and personnel requirements is to ensure consistent, reliable, and appropriate *use* of a test system by users of the test." H.R. Rep. No. 105-310, at 76 (1997) (emphasis added).

The complementary regulation of devices under one statute and regulation of technicians' use of those devices under another statute has an analogue in the regulation of mammography. The x-rays and other equipment used to perform mammography are regulated as devices under the FDCA because they are intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease. 21 U.S.C. § 321(h). Congress noted that "FDA has regulatory responsibility for the proper manufacture of diagnostic x-ray equipment, including mammography equipment, but no responsibility for overseeing the subsequent use of the equipment." H.R. Rep. No. 102-889, at 15 (1992); *see also* S. Rep. No. 102-448, at 6 (1992). It found that this void contributed to the lack of a "coordinated, comprehensive Federal effort to ensure that all mammographies performed in the U.S. meet high standards," and that "a glaring need exists for comprehensive federal regulation." H.R. Rep. No. 102-889, at 17 & 19. The Mammography Quality Standards Act of 1992 (MQSA) was intended to "address these specific concerns by establishing national uniform quality standards that apply to all facilities." S. Rep. No. 102-448, at 6. Like CLIA, the MQSA establishes a certification requirement (in this case for mammography facilities), as well as inspection requirements, and a directive to the Secretary of

Health and Human Services (HHS) to establish quality standards that include: a requirement that facilities maintain a quality assurance and quality control program; personnel qualification standards; and equipment standards. 42 U.S.C. § 263b(b), (f), & (g); *compare with* 42 U.S.C. § 263a(b), (f), & (g).

Enactment of the MQSA did not repeal FDA's authority to regulate mammography equipment as devices. As described in the legislative history cited above, Congress viewed the FDCA authority to regulate mammography devices and the MQSA authority to regulate use of those devices as complementary and equally necessary. Similarly, FDCA authority to regulate devices used in laboratories and CLIA authority to regulate use of those devices are also complementary and equally necessary. Indeed, in a congressional hearing regarding CLIA, the HCFA Administrator clearly acknowledged FDA's role in regulating devices that are part of laboratory testing: "On the quality issue, first, the Health Care Financing Administration has oversight authority and will use that to do a better job under our new regulations. The role of the Center for Disease Control is to provide expert advice to us on how we regulate labs. The role of the FDA is in oversight of the devices and other technical aspects of lab testing." Statement of Dr. William L. Roper, Administrator, HCFA, Committee Hearing on H.R. 4325 (July 6, 1988), at 77.

ACLA also asserts that Congress did not intend FDA regulation of LDTs because CLIA already requires laboratories to submit to inspections of their "facilities, equipment, materials, records, and information" and includes "enforcement powers paralleling those in the FDCA such as injunction and criminal penalties." Pet. at 11. As a threshold matter, different agencies may in fact share enforcement jurisdiction, such as FDA and the Federal Trade Commission do for deceptive food marketing. *See* 15 U.S.C. § 52(a); 21 U.S.C. §§ 341, 343(a)(2) (foods for special dietary use). In any event, as discussed above, CLIA serves a different purpose than the FDCA and therefore, the inspection and enforcement authorities under the different statutes are focused on different areas. For example, CLIA only provides for injunctions "[w]henever the Secretary has reason to believe that continuation of any *activity by a laboratory* would constitute a significant hazard to the public health." 42 U.S.C. § 263a(j) (emphasis added). By contrast, the FDCA provides for injunctions against prohibited acts in 21 U.S.C. § 331 such as introducing an *adulterated product*, even if those products have not actually been shown to be a significant hazard. 21 U.S.C. § 332 (emphasis added). The FDCA also provides seizure authority for *adulterated or misbranded articles*, which has no parallel in CLIA. 21 U.S.C. § 334 (emphasis added). Moreover, the MQSA, which regulates facilities that offer mammography services using mammography equipment, includes the authority to inspect the facilities and their "equipment, materials, records, and information" and enforcement powers paralleling those in the FDCA, such as civil money penalties and injunction. 42 U.S.C. § 263b(g), (h) & (j). However, as discussed above, enactment of the MQSA did not repeal FDA's authority to regulate mammography equipment as devices.

Further, "[i]t is well established that when Congress revisits a statute giving rise to a longstanding administrative interpretation without pertinent change, the 'congressional failure to revise or repeal the agency's interpretation is persuasive evidence that the interpretation is the one intended by Congress.'" *CFTC v. Schor*, 478 U.S. 833, 846 (1986) (citation omitted). Although FDA has been generally exercising enforcement discretion with respect to LDTs, the

agency made clear in the late 1990s that it may regulate LDTs under the FDCA. For example, in 1998, in response to a citizen petition requesting that FDA not regulate LDTs (also referred to as "in-house" or "home brew" assays), FDA unequivocally stated: "[FDA] may regulate assays developed by clinical reference laboratories strictly for in-house use as medical devices." Letter from D. Bruce Burlington, M.D., Director, FDA/CDRH, to Jeffrey N. Gibbs, Esq., Hyman, Phelps & McNamara, P.C., Docket No. 92P-0405 (August 12, 1998) (HPM Citizen Petition Response). Since the late 1990s, the FDCA has been amended at least 10 times and the device-related provisions in particular were significantly amended by the Medical Device User Fee and Modernization Act of 2002 (Pub. L. No. 107-250), the Food and Drug Administration Amendments Act of 2007 (Pub. L. No. 110-85), and the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA) (Pub. L. 112-144). Despite many opportunities to revise or repeal FDA's interpretation of its authority under the FDCA with respect to LDTs, Congress took no such action. Notably, FDASIA was enacted after FDA announced in 2010 its intention to reconsider its policy of enforcement discretion for LDTs and develop a risk-based oversight framework for LDTs. 75 FR 34463 (June 17, 2010). Congress was clearly aware of FDA's intention but did not in any way limit FDA's authority to regulate LDTs; instead, Congress included a provision in FDASIA requiring prior notice to Congress with respect to any draft or final guidance on the regulation of LDTs. Section 1143 of FDASIA, Pub. L. 112-144, 126 Stat. 1130.

D. CLIA regulations are consistent with FDA's regulations that apply to LDTs

CMS has interpreted its own authority under CLIA in conformity with congressional intent. Contrary to ACLA's assertion that "FDA regulation of LDTs is inconsistent with CMS regulations under CLIA," Pet. at 11, in the preamble to the final rules implementing CLIA, CMS stated, in direct and unequivocal language: "CLIA specifically requires the regulation of the provision of laboratory services. On the other hand, CLIA and those implementing regulations are not intended to affect FDA's existing jurisdiction under the [FDCA] to regulate devices, products used by providers of laboratory services." 57 FR 7002, 7010 (Feb. 28, 1992). CMS has stated clearly that its authority under CLIA differs from FDA's authority under the FDCA to regulate devices.

FDA has also repeatedly interpreted the authority Congress gave it to encompass all IVDs, including those that are manufactured by laboratories. As mentioned above in Section III.1.C., FDA stated in its response to a citizen petition in 1998, "[FDA] may regulate assays developed by clinical reference laboratories strictly for in-house use as medical devices." HPM Citizen Petition Response. In promulgating the analyte specific reagent (ASR) regulation, FDA stated that laboratories that develop tests "are acting as manufacturers of medical devices and are subject to FDA jurisdiction under the act." 62 FR 62243, 62249 (Nov, 21, 1997). Although FDA chose not to extend the scope of the ASR rule to laboratory-developed ASRs, it made clear that such products are subject to FDA jurisdiction. *Id.* The agency reiterated this view in the preamble to the rule reclassifying and restricting over-the-counter (OTC) test sample collection systems for drugs of abuse testing, when it stated "in-house (home brew) laboratory tests are medical devices subject to regulation by FDA. FDA considers clinical laboratories that develop such tests to be acting as manufacturers." 65 FR 18230, 18231 (April 7, 2000). In the same

preamble, FDA differentiated its review function under the FDCA from the review function under CLIA, noting that, while "CLIA requirements focus on the proficiency of the laboratories performing tests," FDCA requirements "address issues related to device safety and effectiveness outside the usual CLIA review program." *Id.*

Moreover, the CLIA regulations themselves reveal that CMS performs a different function under CLIA than FDA does under the FDCA. CMS requires that laboratories that modify an FDA cleared/approved test, or develop a test that is not FDA cleared/approved, establish performance specifications for such factors as accuracy, precision, analytical sensitivity, analytical specificity, reportable range of test results, reference intervals, and "any other performance characteristic required for test performance." 42 CFR 493.1253(b)(2). These requirements address the laboratory's ability to perform the test in an accurate and reliable manner and whether the test finds what it is supposed to find (i.e., the analyte it is intended to detect) on a consistent basis. Although these requirements include establishing performance specifications for analytical sensitivity and specificity, as discussed further below in Section 4.A., CLIA inspections determine whether analytical validation was carried out, but do not closely examine the data from the validation, which may uncover errors in test design or other problems. Therefore, CLIA inspections do not assess analytical validation for purposes of determining the safety and effectiveness of the test as FDA does. *See* Laboratory Developed Tests: Frequently Asked Questions, available at http://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/LDT-and-CLIA_FAQs.pdf. More importantly, these requirements do not address the ability of the test to accurately detect or predict the risk of the particular disease or condition for which the test is offered, and thus, CMS does not examine the clinical validity of tests as FDA does.[9] *See* 21 U.S.C. §§ 360c, 360e and 21 CFR 814.20, 860.7 (FDA requirements to establish reasonable assurance of safety and effectiveness); CLIA Overview and Laboratory Developed Tests: Frequently Asked Questions, available at http://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/LDT-and-CLIA_FAQs.pdf. As the HHS Secretary's Advisory Committee on Genetic Testing (SACGT) stated in the context of genetic tests, initial knowledge of the clinical validity of a test "is essential to assess its safety and efficacy." *Enhancing the Oversight of Genetic Tests: Recommendations of the SACGT* (July 2000), at ix, available at http://oba.od.nih.gov/oba/sacgt/reports/oversight_report.pdf.

Further reinforcing that CMS performs a different function under CLIA than FDA does under the FDCA, the CLIA regulations also require that each laboratory that "introduces an unmodified FDA-cleared or approved test . . . [d]emonstrate that it can obtain performance specifications comparable to those established by the manufacturer" for accuracy, precision, and reportable range of test results for the test system, among other requirements. 42 CFR 493.1253(b)(1). These requirements address the laboratory's ability to perform the FDA cleared/approved test in an accurate and reliable manner. CMS explained that with regard to unmodified FDA cleared/approved tests, these requirements ensure that the laboratory has "verified that it can

[9] Indeed, CMS added "analytical" before "sensitivity" and "specificity" in response to comments suggesting that CMS clarify that the agency was not referring to "diagnostic" (i.e., clinical) sensitivity and specificity. 57 FR 7002, 7064 (Feb. 28, 1992).

obtain the manufacturer's performance specifications in the laboratory's environment using the laboratory's testing personnel." 68 FR 3640, 3655 (Jan. 24, 2003). Additionally, CLIA regulations require elements like proficiency testing and periodic function checks to ensure that the test equipment is functioning properly, even when using FDA cleared/approved tests. 42 CFR Part 493 Subpart H and 493.1254.

FDA and CMS regulations embody the position that regulation of both the IVDs themselves and their use in laboratories is necessary to ensure accurate and reliable test results and that, consequently, both of these regulatory schemes are necessary to protect the public health.

E. Commercial distribution is not a prerequisite for FDA jurisdiction under the Act and regardless, LDTs are in commercial distribution

ACLA contends that "LDTs do not entail the prerequisite for FDA jurisdiction under the Act: commercial distribution," referring to section 510(k) of the Act, 21 U.S.C. § 360(k).[10] Pet. at 11. Commercial distribution is not a prerequisite for FDA jurisdiction under the Act. Under section 513(f)(1) of the FDCA, 21 U.S.C. § 360c(f)(1), a postamendment device, i.e., a device that was "not introduced or delivered for introduction into interstate commerce for commercial distribution before [May 28, 1976]," is a class III device by operation of law.[11] Under section 515(a) of the FDCA, 21 U.S.C. § 360e(a), a class III device is required to have an approved premarket approval application (PMA) unless the device satisfies the investigational device exemption (IDE) requirements. In the context of these statutory provisions, "commercial distribution" distinguishes those devices that are "preamendment" and could, for the time-being, remain on the market without a PMA,[12] from those devices that are "postamendment" and must have an approved PMA unless FDA grants a petition for *de novo* classification, reclassifies the

[10] Section 510(k) states in relevant part: Report preceding introduction of devices into interstate commerce. 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 or person who is accredited under section 523(a) [21 U.S.C. § 360m(a)] (in such form and manner as the Secretary shall by regulation prescribe)--

(1) the class in which the device is classified under section 513 [21 U.S.C.§ 360c] or if such person determines that the device is not classified under such section, a statement of that determination and the basis for such person's determination that the device is or is not so classified, and

(2) action taken by such person to comply with requirements under section 514 or 515 [21 U.S.C. § 360d or § 360e] which are applicable to the device. (Emphasis added.)

[11] A postamendment device remains in class III unless and until: (1) the device is classified as class I or II under section 513(f)(2) of the Act, 21 U.S.C. § 360c(f)(2); (2) the device is reclassified into class I or II under section 513(f)(3) of the Act, 21 U.S.C. § 360c(f)(3); or (3) FDA issues an order determining that the device is substantially equivalent, in accordance with section 513(i) of the Act, 21 U.S.C. § 360c(i), to a legally marketed predicate device. 21 U.S.C. § 360c(f)(1).

[12] Preamendment class III devices may remain on the market without an approved PMA unless and until FDA issues an order requiring premarket approval for the device. 21 U.S.C. § 360e(b).

device, or finds the device to be substantially equivalent to a legally marketed predicate device.[13] "Commercial distribution," in other words, is required for a device to qualify as "preamendment" but is not required for a device to qualify as "postamendment." All devices that do not qualify as "preamendment" are automatically "postamendment" whether or not they have been or will be commercially distributed. As such, they are automatically class III by operation of law and must have an approved PMA unless FDA grants a petition for *de novo* classification, reclassifies the device, or finds the device to be substantially equivalent to a legally marketed predicate device. Most, if not all, LDTs that are currently on the market are not preamendment devices but postamendment devices, and therefore, automatically class III by operation of law and subject to the PMA requirements under the Act, without regard to commercial distribution.[14]

Relevant statutory enforcement provisions also indicate that "commercial distribution" is not needed to trigger the PMA requirements. Section 501(f)(1)(B), 21 U.S.C. § 351(f)(1)(B), deems adulterated, without reference to "commercial distribution," any device that is classified into class III under section 513(f) and is required to have an approved PMA under section 515(a), unless the device satisfies the investigational device exemption requirements. Simply put, any requirement of commercial distribution is conspicuously absent from the statutory provisions that require an approved PMA for a postamendment class III device and that render the device adulterated in its absence. Further, FDA may initiate seizure of an adulterated device regardless of whether the device is in commercial distribution. 21 U.S.C. § 334(a)(2)(D) (stating that any adulterated device "shall be liable to be proceeded against at any time on libel of information and condemned in any district court of the United States . . . within the jurisdiction of which they are found," without reference to "commercial distribution").

Regardless, LDTs are in commercial distribution. "Commercial distribution" is defined by regulation as "any distribution of a device intended for human use which is held or offered for sale . . ."[15] 21 CFR 807.3(b). The plain meaning of "distribution" includes "the marketing or

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[13] If a postamendment class III device is determined to be substantially equivalent to a preamendment class III device or one of its substantially equivalent successors, and FDA has not issued an order requiring premarket approval for the device, it may enter the market without an approved PMA. 21 U.S.C. § 360e(b).

[14] However, as with any other postamendment device, an approved PMA will not be required if the LDT is granted a petition for *de novo* classification, is reclassified, or is determined to be substantially equivalent to a legally marketed predicate device. Many legally marketed postamendment devices that have undergone FDA premarket review enter the market through a substantial equivalence determination or *de novo* classification; in other words, only a small percentage of devices enter the market through the PMA process.

[15] Courts have interpreted "held for sale," which also appears in section 301(k) of the FDCA, 21 U.S.C. § 331(k), expansively to include a physician's use or administration of adulterated and/or misbranded drugs or devices to treat patients so that the FDCA's overriding purpose of protecting the public health may be fulfilled. *See, e.g., United States v. Evers*, 643 F.2d 1043, 1050 (5th Cir. 1981) (stating that physicians holding drugs for use in their practice may be considered to hold them for sale within the meaning of section 301(k) of the FDCA); *United States v. Diapulse Corp. of America*, 514 F. 2d 1097, 1098 (2d Cir. 1975) ("devices, used in the treatment of patients, may properly be considered 'held for sale' within the meaning of the Food, Drug, and Cosmetic Act."); *see also Regenerative Sciences*, 878 F. Supp. at 258 ("Defendants create the cell product, the 'drug' in this case, and use it to treat their patients. Such conduct satisfies the 'held for sale' requirement of the [FDCA]."), *aff'd* 741 F.3d at 1320-21.

merchandising of commodities."[16] Merriam-Webster's Collegiate Dictionary (11th ed. 2004). Further, as noted by ACLA, Pet. at 12, the House Report to the MDA provides that "'[c]ommercial distribution' is the functional equivalent of the popular phrase 'on the market.'" H.R. Rep. No. 94-853 at 36 (1976). Consistent with the plain meaning of the term and congressional intent, FDA has interpreted "commercial distribution" to mean "on the market." *See United States v. An Article of Device Consisting of 1,217 Cardboard Boxes*, 607 F. Supp. 990, 994-95 (W.D. Mich. 1985) (according substantial deference to FDA's reasonable interpretation of "commercial distribution" to mean, "in its popular sense, 'on the market'"). Further, FDA's compliance policy guide (CPG) on commercial distribution, cited by ACLA, explains that FDA considers a device to be in commercial distribution, "even though no units of the device had been delivered to purchasers or consignees," if the specified criteria are met. CPG Sec. 300.600 Commercial Distribution with Regard to Premarket Notification (Section 510(k)) (issued July 28, 1978, reissued Sep. 24, 1987). The criterion in the CPG that the manufacturer had accepted or been prepared to accept at least one purchase order "*generally* with delivery to occur immediately or at a promised future date" indicates that delivery is typical but not necessary for "commercial distribution." *Id.* (emphasis added).

LDTs are "on the market" because similar to other IVDs, they are offered commercially for use in the diagnosis/treatment of patients. Like other IVDs, laboratories often promote their LDTs on their website for the diagnosis/treatment of various diseases and conditions. Additionally, while delivery is not necessary for commercial distribution, some laboratories manufacture their own collection kit/system which they ship to physicians ordering their test to collect the specimen for testing. Further, some LDTs incorporate software that analyzes the test results and generates individualized test reports that are delivered to the ordering physician for use in patient diagnosis/treatment. LDTs that are offered commercially for use in the diagnosis/treatment of patients are therefore in commercial distribution and subject to the requirements of section 510(k) of the FDCA, 21 U.S.C. § 360(k), and FDA's implementing regulations in 21 CFR Part 807, among other requirements.[17]

F. FDA may modify its enforcement discretion policy for LDTs through guidance

a. An agency enforcement policy is a general statement of policy and therefore, exempt from rulemaking

Additionally, ACLA claims that "an attempt to regulate LDTs through guidance documents would be inappropriate." Pet. at 13. As stated in the agency's prior response to a citizen petition regarding LDTs, FDA "may regulate assays developed by clinical reference laboratories strictly

[16] The definition of "commodity" includes "something useful or valued." Merriam-Webster's Collegiate Dictionary (11th ed. 2004).

[17] Additionally, under section 709 of the FDCA, in any action to enforce the requirements of the Act respecting an FDA-regulated article, "the connection with interstate commerce required for jurisdiction in such action shall be presumed to exist." 21 U.S.C. § 379a.

for in-house use as medical devices" and "has the authority to provide guidance to industry . . . addressing or referring to in-house assays." HPM Citizen Petition Response.

As noted by ACLA in Section II of its petition, FDA has consistently maintained its authority to regulate LDTs under the FDCA for many years but has chosen to exercise enforcement discretion and generally not enforced applicable provisions under the FDCA and FDA regulations with respect to LDTs. *See, e.g.*, 62 FR 62243, 62249 (1997) ("FDA believes that clinical laboratories that develop [in-house] tests are acting as manufacturers of medical devices and are subject to FDA jurisdiction under the act."); 64 FR 67273, 67280 (Dec. 1, 1999) ("The FDA has stated that it has authority, by law, to regulate home brew laboratory tests, but the agency has elected, as a matter of enforcement discretion, not to exercise that authority."); 65 FR 18230, 18231 (2000) ("The agency believes that in-house (home brew) laboratory tests are medical devices subject to regulation by FDA. FDA considers clinical laboratories that develop such tests to be acting as manufacturers."); 71 FR 52800, 52801 (Sep. 7, 2006) (FDA "has generally exercised enforcement discretion over laboratory-developed ASRs and laboratory-developed tests that use commercially available and laboratory-developed ASRs."); 75 FR 34463 (June 17, 2010) ("Since the implementation of the Medical Device Amendments of 1976, FDA has generally exercised enforcement discretion and not enforced applicable regulations with respect to LDTs"). However, FDA stated that it may take "measures authorized by law to assure assessment of a test's clinical validity or utility if such measures are needed" and that "at a future date, FDA may reevaluate whether additional controls over the in-house tests are warranted to provide an appropriate level of consumer protection." 62 FR at 62252.

FDA may issue its enforcement policy for LDTs through the guidance process. In accordance with its good guidance practices, FDA communicates its enforcement policies through guidance documents. 21 CFR 10.115(b)(2) and (e). Moreover, an agency enforcement policy is a general statement of policy, and under the Administrative Procedure Act (APA), general statements of policy are exempt from the rulemaking procedures. 5 U.S.C. § 553(b)(3)(A). Although not defined in the APA, the Attorney General's Manual on the Administrative Procedure Act (1947) defines general statements of policy as "statements issued by an agency to advise the public prospectively of the manner in which the agency proposes to exercise a discretionary power." *Id.* at 30, n.3. The decision regarding when to exercise enforcement discretion with respect to LDTs, which FDA has always maintained are within its jurisdiction and subject to the FDCA, is committed to agency discretion by law. *See Heckler v. Chaney,* 470 U.S. 821 (1985).

Further, the court in *Syncor Int'l Corp. v. Shalala*, 127 F.3d 90, 94 (D.C. Cir. 1997), described agency policy statements as follows:

> An agency policy statement does not seek to impose or elaborate or interpret a legal norm. It merely represents an agency position with respect to how it will treat – typically enforce – the governing legal norm. By issuing a policy statement, an agency simply lets the public know its current enforcement or adjudicatory approach. The agency retains the discretion and the authority to change its position – even abruptly – in any specific case because a change in its policy does not effect the legal norm.

A guidance on the agency's enforcement policy with respect to LDTs would fit squarely within these descriptions of agency policy statements. Any such guidance would not establish any legal obligations; FDA's authority over LDTs and the regulatory requirements derive from the FD&C Act. *See Takhar v. Kessler*, 76 F.3d 995, 1002 (9th Cir. 1996) (stating that the challenged FDA compliance policy guides "merely set forth which instances of such illegal use the FDA is likely to view as requiring it to take enforcement action and which instances, while technically violative of the statute, will not ordinarily be subject to enforcement action" and therefore, "do not create any obligations or rights with respect to extra-label veterinary drug use" because "[i]t is the FDCA itself that makes such use illegal."). Any such guidance would modify the agency's prior policy of generally exercising enforcement discretion with respect to LDTs, but as the court stated in *Syncor*, the agency has the authority and discretion to change its policy.

Indeed, the Supreme Court stated in *FCC v. Fox Television States, Inc.*, 556 U.S. 502, 515 (2009), that the APA "makes no distinction . . . between initial agency action and subsequent agency action undoing or revising that action."[18] Applying this principle to agency policy statements, a subsequent policy undoing or revising a prior policy should be exempt from rulemaking just as the prior policy was exempt. Further, in *FCC v. Fox*, the FCC gradually expanded its enforcement of a statutory prohibition against indecent broadcasts. 556 U.S. at 507. The Court held that an FCC order adequately explained the agency's new policy, and that the APA did not require a more substantial explanation or heightened review for such a change. *Id.* at 514-15, 517. Similarly, FDA plans to expand its enforcement under the FDCA with respect to LDTs, and explain why the change is appropriate to protect the public health. FDA has announced similar changes to its enforcement policy for other regulated products in guidance documents.[19] This type of document gives the agency important flexibility to change its enforcement priorities to address developing public health concerns.

ACLA cites *Syncor* to support its argument that issuing a guidance document would be inappropriate but the situation with LDTs is distinguishable from the situation in *Syncor*. In *Syncor*, FDA had stated in a guideline published in 1984 that the pharmacy exemption applied to nuclear pharmacies that compounded positron emission tomography (PET) pharmaceuticals and therefore, the new drug provisions of the FDCA did not apply to them. *Id.* at 93, 95. However, in a subsequent notice in 1995, the agency changed its view and asserted that such pharmacies were subject to the new drug provisions of the FDCA. *Id.* at 92. The court stated: "Their activities -- which clearly fell within the scope of the regular course of the practice of the profession of pharmacy in 1984 -- are thought no longer to fall within that scope. This is not a change in interpretation or in enforcement policy, but rather, is fundamentally new regulation."

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[18] *See also Vermont Yankee Nuclear Power Corp. v. Natural Resources Defense Council, Inc.*, 435 U.S. 519, 524 (1978) (holding that the APA established the maximum procedural requirements imposed on agencies in conducting rulemaking and except in "extremely rare" circumstances, courts are "not free to impose" any "additional procedural rights" beyond those set forth in the APA).

[19] *See* Compliance Policy Guidance Sec. 440.100, Marketed New Drugs Without Approved NDAs and ANDAs (Sept. 19, 2011), *available at* http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074382.htm; *see also United States v. Sage Pharms.*, 210 F.3d 475, 479 (5th Cir. 2000) (discussing FDA's enforcement policy for unapproved new drugs favorably).

Id. at 95. Unlike the situation in *Syncor*, FDA has not changed its view regarding whether LDTs are subject to the FDCA. As stated above, the agency has consistently maintained that LDTs are devices and laboratories that manufacture LDTs are device manufacturers subject to FDA regulation under the FDCA.

b. Even assuming that a change in enforcement policy for LDTs would have a substantial impact, simply because agency action has substantial impact does not mean it is subject to rulemaking if it is otherwise exempt from the APA

ACLA also claims that "an attempt to regulate LDTs through guidance documents would be inappropriate" because "FDA would be asserting jurisdiction over an entire industry sector, which would have a major impact on the economy." Pet. at 13. FDA has been asserting jurisdiction over LDTs and laboratories that manufacture LDTs but has generally exercised enforcement discretion so that the agency has generally not enforced applicable provisions under the FDCA and FDA regulations with respect to LDTs. However, whether or not a change in enforcement policy for LDTs would have a substantial impact, simply because agency action has substantial impact does not mean it is subject to rulemaking if it is otherwise exempt from the APA.

ACLA cites several cases and quotes certain phrases from those cases that seemingly indicate that agency statements that have an impact on private parties require rulemaking. Pet. at 13. The phrases are quoted out of context, and the cases cited do not stand for this proposition. In *Gen. Elec. Co. v. EPA*, 290 F.3d 377, 383 (D.C. Cir. 2002), the language about a document having binding effect if affected parties are reasonably led to believe that failure to conform will bring adverse consequences is in the context of a discussion about how mandatory language in a document can be sufficient to render it binding. In this case, the court pointed to the mandatory language in EPA's guidance document and held that the guidance itself imposed binding obligations on applicants by requiring them to conform to one of the two methods specified in the guidance for conducting polychlorinated byphenyls (PCB) risk assessments. *Id.* at 384. In *Chamber of Commerce v. Dept. of Labor*, 174 F.3d 206, 211-13 (D.C. Cir. 1999), the court considered whether OSHA's Directive had a "substantial impact" on employers to determine whether it was a procedural rule, which does not alter the rights or interests of private parties, and did not even consider "substantial impact" in determining whether it was a statement of policy. The court concluded that the Directive was neither a procedural rule nor a policy statement, and therefore, it was subject to notice-and-comment rulemaking under the APA. *Id.* at 213.

ACLA also cites *Thomas v. New York*, 802 F.2d 1443, 1447 (D.C. Cir. 1986), in which the court held that if the prior EPA Administrator's findings "*forced* the EPA to take direct and substantial regulatory actions," they could not be promulgated without rulemaking. Pet. at 13 n.76. In particular, ACLA refers to a note in that case but *Cabais v. Egger*, 690 F.2d 234, 237 (D.C. Cir. 1982), which is cited in that note, explained: "Simply because agency action has substantial impact does not mean it is subject to notice and comment if it is otherwise expressly exempt under the APA. In other words, as an independent basis for determining the applicability of APA procedures, the substantial impact test has no validity." Further, in *Brock v. Cathedral Bluffs Shale Oil Co.*, 796 F.2d 533, 537 (D.C Cir. 1986) (citation omitted), the court stated, "An agency

pronouncement is not deemed a binding regulation merely because it may have 'some substantive impact,' as long as it 'leaves the administrator free to exercise his informed discretion.'" In this case, the court held that the Secretary of Labor's enforcement policy, which described those situations in which citation of production-operators for violations involving their independent contractors was "ordinarily" appropriate, was a statement of policy, not a binding rule, stating: "The language of the guideline is replete with indications that the Secretary retained his discretion to cite production-operators as he saw fit. . . . Our decision on this point is reinforced by the fact that the statement here in question pertains to an agency's exercise of its enforcement discretion -- an area in which courts have traditionally been most reluctant to interfere." *Id.* at 538.

c. Laboratories that manufacture LDTs do not fall within the exemptions from registration

ACLA further claims that "an attempt to regulate LDTs through guidance documents would be inappropriate" because "[d]irecting clinical laboratories to register as device establishments would violate the existing FDA regulation that exempts clinical laboratories from registration." Pet. at 13. ACLA cites 21 CFR 807.65(f) and (i) to support its claim. These regulations exempt from registration "[p]ersons who manufacture, prepare, propagate, compound, or process devices solely for use in research, teaching, or analysis and do not introduce such devices into commercial distribution," and "[p]ersons who dispense devices to the ultimate consumer or 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 hearing aid dispenser, optician, *clinical laboratory*, assembler of diagnostic x-ray systems, and personnel from a hospital, clinical, dental laboratory, orthotic or prosthetic retail facility, whose primary responsibility to the ultimate consumer is to dispense or provide a service through the use of a *previously manufactured device*" (emphasis added), respectively. Laboratories that manufacture and offer LDTs do not fall within these exemptions.

The exemption in 21 CFR 807.65(f) reflects the provision in the FDCA that exempts from registration persons who manufacture devices "solely for use in research, teaching, or chemical analysis and not for sale," 21 U.S.C. § 360(g)(3), and thus applies only to persons who manufacture devices solely for these limited, nonclinical, noncommercial uses. Therefore, this exemption does not apply to laboratories that manufacture and offer devices commercially for use in clinical diagnosis/treatment. In addition, the exemption in 21 CFR 807.65(i) applies only to persons who dispense devices to the ultimate consumer or who provide a service *using a previously manufactured device*, and therefore, does not apply to persons who manufacture and offer their own devices. A clinical laboratory that conducts testing using legally marketed tests purchased from a device manufacturer would fall within the exemption in 21 CFR 807.65(i) but a clinical laboratory that manufactures its own tests and conducts testing using such tests would not fall within this exemption.

2. FDA regulation of LDTs would protect the public health

ACLA claims that "FDA's regulation of LDTs as devices would adversely affect patient care in the United States." Pet. at 13. On the contrary, FDA oversight of LDTs would protect the public health by providing for the safety and effectiveness of these tests which are often used in making critical health care decisions. As discussed in Section I above, there have been significant changes over the years with respect to the laboratories that manufacture and offer LDTs, the tests themselves, and their role in clinical decision-making. Many clinical laboratories today are, or are a part of, corporations that offer their LDTs nationally rather than local institutions that offer LDTs to serve the needs of a local patient population. Current LDTs often incorporate sophisticated technology to generate test results and clinical interpretations, and are often used to assess common diseases and conditions, including those that are serious and life-threatening, and to inform critical treatment decisions. Further, even when FDA approved/cleared tests are available for a disease or condition, laboratories often choose to manufacture and offer their own tests which have not been independently evaluated by FDA for safety and effectiveness.[20]

Given these changes, FDA oversight of LDTs is necessary to protect the public health. Without FDA oversight, there is no assurance that LDTs are safe and effective for their intended use in clinical diagnosis/treatment. While it is important that patients have access to tests that benefit the public health, there is no benefit – and there may be harm – to patients when tests that are not safe and effective are used in patient care. The risks associated with unsafe/ineffective LDTs are much greater today given their widespread use for common diseases and conditions, including those that serious and life-threatening, and their use in critical treatment decisions. For example, incorrect diagnosis due to the use of unsafe/ineffective LDTs that are intended to guide treatment decisions put patients at risk of receiving the wrong treatment (either a drug or medical procedure) or a harmful treatment; incorrectly diagnosed patients may also not receive appropriate, life-saving treatment. Because there is no adverse event reporting requirement under CLIA, and because FDA has been generally exercising enforcement discretion with respect to the manufacturer medical device reporting (MDR) requirement under the FDCA, there are not sufficient data on the number of unsafe/ineffective LDTs that have caused or could cause harm. However, there have been reports about the lack of adequate validation for certain tests manufactured and offered by laboratories. *See, e.g.,* Buchen, L. Nature, *Missing the mark. Why is it so hard to find a test to predict cancer?* 471: 428-432 (Mar. 2011), at www.nature.com/news/2011/110323/full/471428a.html?s=news_rss;[21] CDC,

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[20] In addition to the lack of any safety and effectiveness evaluation, FDA is concerned that the current enforcement discretion policy for LDTs and the increasing use of LDTs even when a FDA approved/cleared test is available may create disincentives for other device manufacturers to invest in IVD development. Stakeholders have raised similar concerns. *See, e.g.,* Combination Products Coalition Comment, at 13-14 (stating that "if the LDT manufacturer can ride the coattails of an FDA-approved IVD and avoid the same cost of market entry, it will be difficult for IVD developers to continue putting resources into IVD development").

[21] This article discusses the OvaSure test which was offered in June 2008 by Laboratory Corporation of America (LabCorp) for the assessment of the presence of early stage ovarian cancer in high-risk women. *See LabCorp Announces Availability of OvaSure(TM)* (June 23, 2008), at http://www.reuters.com/article/2008/06/23/idUS203428+23-Jun-2008+BW20080623. Although FDA did not consider OvaSure to be a true LDT, it was offered as an LDT and did not undergo FDA premarket review. A week after LabCorp's announcement of OvaSure's availability, the Society of Gynecologic Oncologists in Chicago, Illinois released a statement expressing concern about OvaSure stating that "additional research [was] needed to validate the test's effectiveness." *See* Buchen, L. Nature, *Missing the mark. Why is it so hard to find a test to*

Morbidity and Mortality Weekly Report (MMWR), *Caution Regarding Testing for Lyme Disease*, at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5405a6.htm.

ACLA raises concerns about the impact of FDA oversight on the availability of LDTs for rare diseases or conditions and LDTs that serve unmet healthcare needs. Pet. at 14-15. FDA recognizes that in developing an oversight framework for LDTs, there are important considerations that should be taken into account. For this reason, FDA held a public meeting in 2010 to discuss issues and stakeholder concerns regarding any such oversight framework and provided additional opportunity for comment through a public docket. *See* 75 FR 34463. These specific concerns were raised at the meeting and in comments to the public docket. FDA intends to address these concerns and other important considerations in its proposed enforcement policy for LDTs, and will provide an opportunity for comment on the proposed policy in accordance with good guidance practices.

Additionally, ACLA asserts that "CLIA affords laboratories the flexibility to develop tests quickly and to update them regularly" and that "FDA regulation of LDTs . . . would slow the availability of novel tests" and "slow improvements in existing tests." Pet. at 15. Comparing regulation under CLIA and the FDCA is inapt because these two statutes serve different purposes and focus on different areas. As discussed in Sections III.1.C, III.1.D., and III.4, CLIA addresses how laboratories conduct testing but does not provide for the safety and effectiveness of the tests themselves. LDTs that incorporate new or improved technology only benefit the public health if they are safe and effective for their intended use in clinical diagnosis/treatment. As a general approach, FDA tries to foster innovation and improvements in medical technology while assuring safe and effective medical devices.

ACLA also expresses concern that FDA oversight of LDTs would create an "immense workload" that would slow premarket review and delay the availability of new tests. Pet. at 15. FDA believes any such concern can be addressed by taking a phased in approach to enforcement. FDA intends to take such an approach so that premarket review of LDTs can be handled with available resources and in accordance with the agency's performance goals. A phased in approach to enforcement would also provide laboratories with an opportunity to prepare appropriate premarket submissions for their LDTs and meet other applicable regulatory requirements under the FDCA.

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predict cancer? 471: 428-432 (2011), at www.nature.com/news/2011/110323/full/471428a.html?s=news_rss. FDA also expressed concern that this high risk test was not supported by adequate clinical validation and may harm the public health, and issued a warning letter to LabCorp stating that OvaSure was a device requiring premarket clearance/approval under the FDCA. *See* FDA Letter to LabCorp (Aug. 2008) at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm125130.htm; FDA Warning Letter to LabCorp (Sep. 2008) at http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2008/ucm1048114.htm. LabCorp disagreed but decided to stop offering OvaSure in October 2008. *See* Nature, *Missing the mark. Why is it so hard to find a test to predict cancer?* A few years later, a study coordinated by the National Cancer Institute showed that the six biomarkers used in the OvaSure test detected ovarian cancer in only 34% of the women who were diagnosed with the disease within a year. *See id*; Zhu, C.S. et al. Cancer Prev. Res., *A framework for evaluating biomarkers for early detection: validation of biomarker panels for ovarian cancer*, 4:375-383 (2011). Although FDA did not consider OvaSure to be a true LDT, the OvaSure example illustrates the need for appropriate FDA oversight to assure that tests offered by laboratories are safe and effective for their intended use in clinical diagnosis/treatment.

ACLA also claims that "FDA approval/clearance process is not designed to allow for the rapid clearance or approval of tests for patients with emergent infectious diseases." Pet. at 15. An expedited process, however, does exist under the FDCA to allow for rapid review of devices to address public health emergencies involving emergent infectious diseases. Congress provided FDA with the authority to issue Emergency Use Authorization (EUA) to authorize the use of an unapproved medical device or an unapproved use of an approved medical device during a declared emergency. *See* 21 U.S.C. § 360bbb-3. Under this authority, FDA issued EUAs for IVDs for the diagnosis of various diseases or conditions, including emergent infectious diseases such as the H7N9 avian influenza virus and the H1N1 influenza virus within a few days of the Secretary's declaration of a public health emergency (FDA issued an EUA for an IVD for the H7N9 avian influenza virus three days after the Secretary's declaration and an EUA for an IVD for the H1N1 influenza virus six days after the Secretary's declaration). *See* FDA's Emergency Use Authorizations webpage at http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm. Notably, some of the IVDs for which FDA has issued EUAs were LDTs. *See, e.g.*, EUA for the ViraCor 2009 H1N1 Influenza A Real-time RT-PCR test at http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm198465.htm; EUA for DIATHERIX H1N1-09 Influenza Test at http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm186250.htm.

3. Many of the "unintended consequences" asserted by ACLA have to do with legal matters that are outside the scope of FDA's jurisdiction

ACLA contends that "FDA regulation of LDTs as devices would result in numerous unintended consequences with significant economic repercussions for the United States laboratory industry." Pet. at 3. In particular, ACLA claims "FDA's regulation of LDTs as devices could trigger legal obligations far beyond the FDA requirements," including "duplicate taxes by application of the federal medical device tax," "additional state liability laws," and "the Physician Payments Sunshine Act." Pet. at 16-17. The device tax, state liability laws, and the Physician Payments Sunshine Act are administered by other agencies, and are outside the scope of FDA's jurisdiction. However, FDA notes that while the agency has been generally exercising enforcement discretion with respect to LDTs, the agency has consistently maintained that LDTs are devices under the FDCA. *See* Section III.1.F., *supra*. In other words, any change in enforcement policy for LDTs does not alter their regulatory status under the FDCA.

Regarding the concerns raised by ACLA about potential challenges in complying with FDA requirements, Pet. at 17, FDA intends to address many of the concerns in its proposed enforcement policy for LDTs. To the extent that ACLA has concerns not addressed in the draft guidance document, ACLA may submit a comment explaining its concerns so that the concerns may be considered, along with other comments, as part of the guidance process.

4. CLIA regulation does not adequately address FDA's public health concerns for LDTs

A. CLIA is insufficient to provide for safe and effective LDTs

ACLA claims that the "CLIA statute and regulations include safeguards to ensure that LDTs are appropriately validated" and that "regulation of LDTs under CLIA has effectively protected the public health." Pet. at 17-18. As discussed in Sections III.1.C. and III.1.D., CLIA serves a different purpose and does not provide for safe and effective tests. CLIA is insufficient to provide for safe and effective LDTs because: CLIA does not regulate premarket activities; CLIA does not assess clinical validity, which is critical, as analytical validity alone, i.e., accurate detection of the particular analyte of interest, would not ensure that the test would accurately detect or predict the risk of the disease or condition for which the test is offered; CLIA does not regulate the manufacturing of devices, a critical area of control to ensure appropriate test design and consistent manufacture of high-quality tests; CLIA does not provide for human subject protections for patients who participate in LDT clinical research trials; and CLIA does not require adverse event reporting, which may identify safety issues and other problems with an LDT. Indeed, because there is no adverse event reporting requirement under CLIA and FDA has been generally exercising enforcement discretion with respect to the manufacturer MDR reporting requirement under the FDCA, systematic data on adverse events have not been collected or reported for LDTs. However, as noted in Section III.2., there have been reports about the lack of adequate validation for certain tests manufactured and offered by laboratories.

The Secretary of HHS' Advisory Committee on Genetics, Health, and Society (SACGHS), which included experts in clinical laboratory practices and other disciplines, also indicated that CLIA is insufficient to provide for safe and effective LDTs. The SACGHS identified clinical validity as an area of particular concern for which oversight of LDTs by FDA was needed. Specifically, the SACGHS found that "[m]ost genetic tests in use today are LDTs and have not been reviewed by FDA," and recommended: "To help close the gaps in oversight related to clinical validity, which would help ensure the appropriate use of laboratory tests, the U.S. Food and Drug Administration (FDA) should address all laboratory tests, regardless of how they are produced (i.e., as a commercial test kit or laboratory-developed test), in a manner that takes advantage of its current experience."[22] *U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services; Report of the Secretary's Advisory Committee on Genetics, Health, and Society* (April 2008) (SACGHS Report[23]), at 39 & 191, available at http://oba.od.nih.gov/oba/SACGHS/reports/SACGHS_oversight_report.pdf.

Additionally, as discussed in Section III.1.D., although CLIA regulations require that performance specifications for analytical sensitivity and specificity be established, the oversight

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[22] Although SACGHS was tasked to look at the oversight of genetic tests, the Committee "concluded that the concerns associated with genetic testing generally do not differ from other complex laboratory tests. For this reason, and because it will be increasingly difficult to distinguish between genetic and other complex laboratory tests, [the Committee] chose to apply a number of [its] recommendations to laboratory tests generally." Letter from SACGHS to Michael O. Leavitt, Secretary of HHS (Apr. 30, 2008), *in U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services; Report of the Secretary's Advisory Committee on Genetics, Health, and Society* (April 2008) (SACGHS Report).

[23] The SACGHS Report represented "the culmination of nearly a year of extensive factfinding, analysis, expert consultation, outreach to the public, and deliberation by the Committee." Letter from SACGHS to Michael O. Leavitt, Secretary of HHS (Apr. 30, 2008), *in* SACGHS Report.

provided by CLIA on analytical validity is in the form of an inspection conducted after an LDT is offered for clinical use, and in the context of an inspection of the entire laboratory. Further, because CLIA addresses the quality of laboratory testing but not the safety and effectiveness of the tests themselves, a CLIA inspection determines whether analytical validation was carried out, but does not uncover errors in test design or other similar problems. *See* Laboratory Developed Tests: Frequently Asked Questions, available at http://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/LDT-and-CLIA_FAQs.pdf. In contrast, FDA premarket review of analytical validity for a test is significantly more comprehensive and in-depth because it is for the purpose of evaluating the safety and effectiveness of the test for its intended use in clinical diagnosis/treatment. In FDA's experience, FDA's premarket review of IVDs frequently uncovers problems with validation and provides the opportunity for the manufacturer to rectify the problems before the test is used in the clinical diagnosis/treatment of patients.

Both the FDCA and CLIA are needed together to assure that test results, whether obtained using an FDA approved/cleared IVD or an LDT, are of high quality.

B. Relying on existing FDA authority is preferable to amending CLIA

ACLA also asserts that "[t]o the extent that stakeholders have concerns about possible gaps in the clinical validation of LDTs, the most logical and appropriate solution would be to amend CLIA and/or its regulations." Pet. at 18. As discussed above, requirements for an assessment of clinical validity is only one of the important differences between the FDCA and CLIA, so CLIA would have to be significantly amended to provide for other important regulatory controls that exist under the FDCA to provide for reasonable assurance of the safety and effectiveness of devices, including adverse event reporting and good manufacturing practice. Amending CLIA, however, to provide for the type of regulatory controls that currently exist under the FDCA would be inefficient, costly, and unreasonable.

Duplicating authorities that currently exist under the FDCA would create inefficiencies in the regulation of IVDs. Creating a new regulatory system for LDTs under CLIA would require CMS to develop an entirely new infrastructure, including developing comprehensive regulations, new policies, and new practices and procedures. CMS would have to hire and train new staff to implement the new regulatory system. Further, because CMS does not address the clinical validity of any test or review any test to assess safety and effectiveness, CMS would have to contract or recruit additional expertise to evaluate clinical validity or other aspects that are part of a safety and effectiveness review for an LDT. It is unreasonable to create a new regulatory system for LDTs under CLIA when FDA already has the authority, expertise, and infrastructure in place, including regulations, policies, and practices, to address the safety and effectiveness of LDTs. Further, the costs to create a new regulatory system for LDTs under CLIA would be high as they would include management, administrative, and training costs, reviewer costs, database development, surveyor program costs, CMS overhead costs, etc.

Therefore, FDA believes that all IVDs intended for use in the diagnosis of diseases or other conditions or in the cure, mitigation, treatment, or prevention of disease should be regulated (as intended by Congress) under one statute, the FDCA, which provides appropriate and adequate

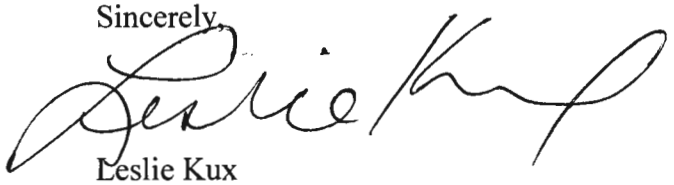
regulatory controls to provide for reasonable assurance of the safety and effectiveness of all devices, including LDTs.

IV. Conclusion

In conclusion, LDTs are devices within the plain language of the definition in the FDCA. Similar to IVD test kits manufactured by other device manufacturers, LDTs are test systems, which contain, among other things, instruments, *in vitro* reagents, and/or other similar or related articles, either produced within the laboratory or purchased from other device manufacturers, that are intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease. The language of CLIA and the FDCA, their legislative history, and CMS' and FDA's interpretations of their respective authorities, support the HHS position that FDA has the authority to regulate LDTs and that the enactment of CLIA and its implementing regulations was not intended to take this authority away from FDA.

FDA has consistently maintained its authority to regulate LDTs under the FDCA for many years but has chosen to exercise enforcement discretion and generally not enforced applicable provisions under the FDCA and FDA regulations with respect to LDTs. However, there have been significant changes in LDTs (e.g., LDTs have become more complex, are often widely offered, and are being increasingly used in guiding critical clinical management decisions) and these changes create potential increased risk for patients. Consequently, FDA plans to change its enforcement discretion policy for LDTs to protect the public health, and may do so through the guidance process. For all the reasons discussed in this response, FDA is denying ACLA's petition.

Sincerely,



Leslie Kux
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