DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
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JUL 31 2014

Daniel J. Popeo
Richard A. Samp
Washington Legal Foundation
2009 Massachusetts Avenue, N.W.
Washington, DC 20036

Re: Docket No. FDA-2006-P-0149

Dear Mr. Popeo and Mr. Samp:

The Food and Drug Administration (FDA, the agency) has reviewed the citizen petition that the Washington Legal Foundation (WLF) submitted on September 28, 2006, pursuant to 21 CFR 10.30. In the petition, WLF requests that FDA "cease and desist" seeking to regulate laboratory-developed tests (LDTs) as medical devices because "FDA does not have the legal authority to regulate these services" and that, if FDA does regulate LDTs as medical devices, it conduct notice-and-comment rulemaking.

FDA has reviewed WLF's petition, as well as 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 Genentech, Inc. (Docket No. FDA-2008-P-0638) and the American Clinical Laboratory Association (Docket No. FDA-2013-P-0667). 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 acknowledging 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

[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.

component, part, or accessory, which is (1) recognized in the official National Formulary, or the 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

WLF argues that (1) "Congress did not assign responsibility for regulating clinical laboratory services and their in-house developed (home brew) assays to FDA under the [FDCA (Federal Food, Drug, and Cosmetic Act)], but to CMS [Centers for Medicare and Medicaid Services] under CLIA [Clinical Laboratory Improvement Amendments of 1988]"; (2) the Secretary of Health and Human Services (HHS) has decided that authority to regulate LDTs "resides with CMS" rather than FDA; and (3) under the Administrative Procedure Act (APA), FDA must promulgate a rule through notice-and-comment rulemaking if it seeks to regulate LDTs. Pet. at 8-17.

1. <u>FDA has jurisdiction over LDTs under the FDCA and FDA's jurisdiction is concurrent and complementary to CMS' jurisdiction over clinical laboratories under CLIA</u>

   A. FDA has jurisdiction over LDTs under the plain language of the FDCA

WLF disputes that FDA has jurisdiction over LDTs because the word "laboratories" does not appear in the MDA. Pet. at 9. But WLF does not dispute that FDA has jurisdiction over other IVDs that otherwise meet the FDCA's definition of device but are not manufactured by laboratories. LDTs are devices within the plain language of the definition. Similar to other IVDs, 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.*

There is nothing in the FDCA statutory language or 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.

B. FDA and CMS have concurrent, complementary jurisdiction over laboratories that manufacture LDTs

WLF's petition also asserts that Congress intended for CMS to assert jurisdiction over LDTs through the Clinical Laboratory Improvement Amendments of 1988 (CLIA or 1988 Amendments), not FDA.[6] Pet. at 8. To the contrary, the history of these statutes supports FDA's

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[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.*

[6] WLF cites *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 132-33 (2000), to support its argument that "Congress has directed in CLIA that CMS shall regulate 'home brew' assays." Pet. at 12. In *Brown & Williamson*, however, the Court found that Congress had precluded FDA from asserting jurisdiction to regulate tobacco products because such authority was inconsistent with congressional intent expressed in the FDCA's overall regulatory

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 CLIA in 1988, 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).[7] 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 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

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scheme and in the tobacco-specific legislation enacted subsequent to the FDCA. *Brown & Williamson*, 529 U.S. at 126. There is no such inconsistency resulting from FDA's authority to regulate LDTs. As discussed in Section III.1.B. of this document, FDA's authority to regulate LDTs is complementary to CMS' authority to regulate clinical laboratories.

[7] 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.

> 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 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.[8] Indeed, in a congressional hearing regarding CLIA, the HCFA

[8] WLF contends that FDA's "assertion of jurisdiction over [LDTs] in many ways parallels the Agency's attempt to establish jurisdiction over drugs compounded by pharmacies," which WLF claims was "rejected" by the district court in *Med. Ctr. Pharm. v. Gonzales*, 451 F. Supp. 2d 854 (W.D. Tex. 2006). Pet. at 13 n.25. In that case, the

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.

C. 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 WLF's contentions, *see* Pet. at 9-10, CMS has stated clearly that its authority under CLIA differs from FDA's authority under the FDCA to regulate devices. 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).

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).[9] These requirements address the

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district court held that compounded drugs are "implicitly exempt" from the "new drug" definition in the FDCA. *Med. Ctr. Pharm.*, 451 F. Supp. 2d at 865. After WLF submitted its petition, however, the district court's decision was vacated on appeal. The Fifth Circuit held that the district court had erred, and that "compounded drugs" indeed are "new drugs" under the FDCA. *Med. Ctr. Pharm. v. Mukasey*, 536 F.3d 383, 405-06 (5th Cir. 2008). The Fifth Circuit further held that under section 503A of the FDCA, 21 U.S.C. § 353a, which was added by the Food and Drug Administration Modernization Act of 1997 (FDAMA), compounded drugs are exempt from the "new drug" approval requirements "[i]f and only if" they satisfy the conditions set forth in that section. *Id.* at 406. In contrast, there is no provision in the FDCA exempting LDTs from the device requirements. Further, as noted in Section III.1.C. of this document, Congress was clearly aware of FDA's intention to reconsider its policy of enforcement discretion for LDTs and develop a risk-based oversight framework for LDTs but did not in any way limit FDA's authority to regulate LDTs; instead, Congress included a provision in the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012 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.

[9] WLF claims that the preamble to the 2003 CLIA regulations refers to "tests *not* regulated by the FDA." Pet. at 10 (emphasis in original). To the extent that WLF is arguing that 42 CFR 493.1253(b)(2) supports a lack of FDA jurisdiction over LDTs, the fact that the CLIA regulations require laboratories to establish performance specifications when the laboratories use a test system that is not FDA cleared/approved does not support a conclusion that FDA cannot regulate LDTs under the FDCA. The requirements in 42 CFR 493.1253(b)(2) were established for CLIA purposes, which as explained in Section III.1.C. above, are different from the FDCA. *See* 68 FR 3640, 3655 (Jan. 24, 2003) ("establishment or verification of performance specifications are integral to the laboratory's establishment of appropriate and effective QC [quality control] and calibration protocols."). Also as explained in Section III.1.C., the provision in 42 CFR 493.1253(b)(2) does not address clinical validity which is essential to the safety and effectiveness of a test.

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, CLIA inspections determine whether analytical validation was carried out, but does 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.[10] *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 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 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.

Moreover, FDA has interpreted its authority under the FDCA to encompass all IVDs, including those that are manufactured by laboratories.[11] Contrary to WLF's claim that FDA is asserting its

[10] 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).

[11] WLF asserts that under FDA's "interpretation of [its] authority, **every** academic medical center, large hospital, and reference laboratory . . . is operating in violation of the [FDCA] . . . and they therefore are subject to enforcement action." Pet. at 12 (emphasis in original). FDA recognizes that in reconsidering its policy of enforcement discretion 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 LDT oversight and provided additional

jurisdiction over LDTs for the "first time," Pet. at 11, the agency has repeatedly stated that LDTs are subject to FDA jurisdiction under the FDCA.[12] FDA stated in a response to a citizen petition in 1998, "[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). 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.*

Further, since the agency made clear in the late 1990s that it may regulate LDTs under the FDCA, Congress could have amended the FDCA to exclude LDTs from the scope of the Act but did not do so. 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). "It is well established that when Congress revisits a statute giving rise to a longstanding administrative interpretation without pertinent change, the 'congressional

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opportunity for comment through a public docket. *See* 75 FR 34463. FDA intends to address various concerns raised by stakeholders, including some of the concerns raised by WLF, 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.

[12] WLF cites the Small Entity Compliance Guidance on ASRs as a statement by FDA that it would not regulate any LDTs, Pet. at 10-11, but WLF misinterprets the statement it cites. This Small Entity Compliance Guidance, among other things, interprets 21 CFR 809.30, a rule that applies only to ASRs offered to laboratories. In particular, Question #4 in this guidance asks what requirements laboratories using ASRs must meet and answers that, among other requirements, the laboratory "must . . . [l]abel the test result to indicate its status as an in-house test in accordance with 21 CFR 809.30(e) as follows: 'This test . . . has not been cleared or approved by [FDA].'" *Analyte Specific Reagents; Small Entity Compliance Guidance; Guidance for Industry* (Feb. 2003) at 3. The next question asks, "Can laboratories add additional labeling or use promotional material to clarify the status of their in-house assays?" *Id.* It is in answer to this question that the guidance states that "laboratories may add information in test reports or in promotional material to clarify that FDA is not requiring the in-house test to go through premarket FDA review." *Id.* In other words, this question and answer segment is in the context of the requirement in 21 CFR 809.30(e) that LDTs manufactured with legally marketed ASRs bear a statement on associated laboratory reports saying that the test is not FDA cleared or approved to inform ordering physicians that the test has not been evaluated by FDA. The fact that FDA issued a rule that imposes such restrictions on certain ASRs does not support a conclusion that FDA cannot regulate any LDTs or that FDA is precluded from exercising its statutory authority to do so.

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). 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.

2. The Secretary has not assigned authority to regulate LDTs to CMS

WLF next argues that the Secretary of HHS has the authority to determine, and has determined, that the authority for regulating LDTs "resides with CMS" under CLIA. Pet. at 14. As explained above, however, in the preambles to both CMS and FDA regulations, the agencies have set forth their position that the focus of CLIA and the FDCA differ. Although CMS does regulate laboratory services under CLIA, CMS has not purported to regulate the safety and effectiveness of devices. *See* 57 FR at 7010; *see also* 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. FDA, likewise, has not indicated that it would cede its authority over device safety and effectiveness to CMS. *See* 65 FR at 18231. Therefore, laboratories that engage in device manufacturing are subject to FDCA device requirements.

Moreover, the Office of the Secretary oversaw the development of both the FDA and the CMS regulations. These 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.

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

WLF alleges that FDA must engage in notice-and-comment rulemaking because, "[u]ntil recently, a well-established FDA policy provided that [laboratory developed] assays were exempt from regulation" and, therefore, "FDA cannot depart from that precedent without" issuing a rule. Pet. at 15-16. WLF is mistaken in this assertion. FDA's official position that LDTs are subject to FDA regulation under the FDCA has been consistent.[13] The agency stated in preambles in

[13] In a comment submitted to the citizen petition docket, Hyman, Phelps & McNamara (the commenter) refers to oral, informal remarks by FDA officials at meetings, none of which affirmatively states that FDA does not have jurisdiction over LDTs or that FDA was exempting LDTs from FDA regulation. Hyman, Phelps & McNamara (HPM), Comment to Docket No. FDA-2006-P-0149, at 10-13. FDA's authoritative statements referenced in Section III.3. of this document stand in marked contrast with the informal remarks cited by the commenter. *N.Y. State Dep't of Soc. Serv. v. Bowen*, 835 F.2d 360, 365 (D.C. Cir. 1987) (contrasting agency's "informal statements" with "position officially articulated"); *see also Paralyzed Veterans of Am. v. D.C. Arena L.P.*, 117 F.3d 579, 587 (D.C. Cir. 1997) ("A speech of a mid-level official of an agency, however, is not the sort of 'fair and considered judgment' that can be thought of as an authoritative departmental position."); 21 CFR 10.85(k) ("A statement made or advice

1997, and again in 2000, that LDTs are devices and clinical laboratories that manufacture them are device manufacturers subject to FDA regulation under the FDCA. 62 FR at 62249 ("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."); 65 FR at 18231 ("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."). In addition, as mentioned above in Section III.1.C., in an 1998 response to a citizen petition requesting that FDA "not regulate as medical devices assays developed by clinical reference laboratories strictly for in-house use," FDA unequivocally stated that "the Commissioner of Food and Drugs may regulate assays developed by clinical reference laboratories strictly for in-house use as medical devices." HPM Citizen Petition Response. Although FDA has generally chosen to exercise its enforcement discretion regarding many LDTs, *see, e.g.*, 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."); 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"), the agency has not instituted a policy of "exempting" such tests from its jurisdiction.[14]

The consistency of FDA's statement of jurisdiction over LDTs distinguishes the agency's action here from the issuance of the notice at issue in *Syncor Int'l Corp. v. Shalala*, 127 F.3d 90 (D.C. Cir. 1997), which is cited by Hyman, Phelps & McNamara (the commenter) in its comment submitted to the citizen petition docket to support the assertion that FDA should engage in rulemaking. 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. 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.* 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." *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

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provided by an FDA employee orally . . . does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.").

[14] The commenter cites FDA's statement in the preamble to the ASR rule (62 FR at 62249) that it was not, as part of that rulemaking, classifying all LDTs as class II or III medical devices as a statement that the agency would *never* regulate *any* LDTs. HPM Comment at 11. This is an incorrect reading of that preamble. FDA's limitation of the scope of the rule to "the classification and regulation of ASR's that move in commerce, not tests developed in-house by clinical laboratories or ASR's created in-house and used exclusively by that laboratory for testing services," was a statement that those products were outside the scope of the rule and not a statement that they were outside of FDA's jurisdiction or authority to regulate. 62 FR at 62249.

regulation under the FDCA. Unlike *Syncor*, there is no "fundamentally new regulation" here. FDA has simply elected to generally exercise enforcement discretion over most LDTs.

However, as mentioned in Section I above, FDA is reconsidering its policy of enforcement discretion for LDTs, and intends to publish its proposed enforcement policy for LDTs in a draft guidance document. As stated in the agency's prior response to a citizen petition regarding LDTs, FDA "has the authority to provide guidance to industry . . . addressing or referring to in-house assays." HPM Citizen Petition Response. 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*, 127 F.3d at 94, 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 for 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."[15] Applying this principle to agency policy

[15] *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

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. 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.[16] This type of document gives the agency important flexibility to change its enforcement priorities to address developing public health concerns.

Finally, FDA has responded to WLF's concern that the public should have an opportunity to comment and "fully appreciate what FDA is attempting to do." Pet. at 15. In response to stakeholders' concern that they have adequate opportunity to provide input, FDA held a public meeting on July 19-20, 2010 to gain input from interested stakeholders on the agency's oversight of LDTs. *See* 75 FR 34463 (June 17, 2010); *see also* FDA's website at http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm212830.htm. The agency also provided additional opportunity for comment through a public docket. *See* 75 FR 34463. FDA has considered the input provided at the meeting and comments provided to the public docket, and plans to provide further opportunity for public comment when it issues a draft guidance outlining the agency's proposed oversight approach for LDTs. FDA intends to address concerns raised by WLF about potential difficulties in complying with FDA's manufacturer medical device reporting requirements in 21 CFR Part 803 and the quality system requirements in 21 CFR Part 820 in its proposed enforcement policy for LDTs. To the extent that WLF has concerns not addressed in the draft guidance document, WLF may submit a comment explaining its concerns so that the concerns may be considered, along with other comments, as part of the guidance process.

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 in regulations and otherwise, support the HHS position that FDA has the authority to regulate LDTs and that the

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rulemaking and except in "extremely rare" circumstances, courts are "not free to impose" any "additional procedural rights" beyond those set forth in the APA).

[16] *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).

enactment of CLIA and its implementing regulations was not intended to take this authority away from FDA. In addition, FDA does not need to undergo notice-and-comment rulemaking to change its enforcement policy; FDA may issue its enforcement policy for LDTs through the agency's guidance process. For all the reasons discussed in this response, FDA is denying WLF's petition.

Sincerely,

Leslie Kux
Assistant Commissioner for Policy