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MUST FDA ENGAGE IN RULEMAKING TO REGULATE LABORATORY-DEVELOPED TESTS?

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VOLUME 1, ISSUE 17 // SEPTEMBER 14, 2011

THE FOOD AND DRUG LAW INSTITUTE
1155 15TH STREET NW, SUITE 800 // WASHINGTON, DC 20005
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Must FDA Engage in Rulemaking to Regulate Laboratory-Developed Tests?

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I. INTRODUCTION

For more than a year, the Food and Drug Administration (FDA) has been signaling plans to develop a risk-based framework for laboratory-developed tests (LDTs), which largely have been outside of the agency's regulatory purview. In July 2010 FDA held a public meeting at which officials unveiled plans to regulate clinical laboratories that develop and perform LDTs as "manufacturers" of medical devices and to subject the LDTs to certain of FDA's medical device requirements, including establishment registration and device listing. More recently, in the context of discussions regarding the reauthorization of the Medical Device User Fee Amendments (MDUFA), FDA confirmed that the agency plans to regulate clinical laboratories and LDTs using a risk-based approach.

FDA officials also have consistently stated that the agency plans to implement its risk-based approach through the issuance of guidance documents, and that it is not required to engage in notice-and-comment rulemaking. This article argues that FDA is legally obligated to proceed through notice-and-comment rulemaking in order to regulate clinical laboratories and the LDTs they develop and perform. Specifically, we argue that since clinical laboratories are exempt from registration and listing requirements under current FDA regulations, requiring them to register and list can be accomplished only through notice-and-comment rulemaking pursuant to the Administrative Procedure Act (APA). Furthermore, in light of FDA's longstanding policy of "enforcement discretion" for LDTs, a policy shift of this magnitude would, under relevant case law, require notice-and-comment rulemaking.

In taking the position that FDA may impose substantive new requirements for clinical laboratories only through rulemaking, we do not address the substantive merits of FDA oversight. We recognize that FDA's proposed involvement in LDT oversight has been, and will continue to be, the subject of robust debate by a wide range of stakeholders. Regardless of where one stands on the substantive issues, however, we hope that all agree that FDA must proceed in accordance with the APA, which is designed to ensure that agency regulations are promulgated in a transparent, deliberate, and equitable manner that is informed by all potentially affected parties and are within the scope of an agency's statutory authority.

POLICY RECOMMENDATIONS

FDA should:

- Discontinue the guidance development process regarding oversight of LDTs
- Engage in rulemaking to depart from longstanding agency practice in the regulation of LDTs.
- Engage with stakeholders throughout the process to understand the impact of FDA regulation on the continued development and availability of validated laboratory tests.

II. BACKGROUND

Clinical laboratories analyze human specimens and provide information to healthcare providers. Clinical laboratory testing has become increasingly important in patient care for a wide range of uses including disease diagnosis, prediction, and prevention and health assessment. In particular, laboratory testing is increasingly used as part of "personalized medicine," to identify patients who will likely benefit from a particular therapy or, alternatively, who may be at greater risk of an adverse reaction.

Clinical laboratories can test specimens using two general approaches. First, for some tests they can purchase a "kit" (in regulatory parlance, an in vitro diagnostic device or IVD) that contains the reagents necessary to perform a particular type of test along with instructions on how to perform the test.[1] Second, the laboratory can develop its own testing protocol and purchase individually the reagents and other materials needed to implement that protocol. This second approach is generally referred to as an LDT.[2] A laboratory may choose to develop an LDT because there is no kit available for the particular test, because the laboratory wants to use a different methodology to perform the test, or for other reasons.

Although there is no comprehensive database that identifies all tests performed by clinical laboratories, it is safe to say that a significant percentage of clinical laboratory tests are performed using LDTs. This is particularly the case with respect to genetic testing. By one estimate, there are now genetic tests for more than 2,000 diseases.[3] Only a handful of these tests are sold as IVDs; the vast majority are LDTs.

III. ISSUES IN DISPUTE

Congress first imposed explicit premarket review requirements on medical devices in 1976.[4] The Medical Device Amendments (MDA) established a risk-based scheme that assigns devices to one of three classes, each of which is subject to a different degree of regulatory control, depending on the risk posed by the device.[5] As a result of the MDA, section 201(h) of the Federal Food, Drug, and Cosmetic Act (FDCA) currently defines the term "device," in relevant part, 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—
>
> …
>
> (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.[6]

FDA began issuing regulations to implement the MDA in 1977. On August 23, 1977, FDA issued regulations, codified at 21 C.F.R. Part 807, setting forth the procedures for the registration of device establishments and for 510(k) premarket notification submissions.[7] At the time FDA issued its device establishment regulations, FDA had already asserted authority over IVD products. Specifically, before the enactment of the MDA, FDA had issued regulations that defined IVD products as:

> those reagents, instruments and systems intended for use in the diagnosis of disease or in the 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 drugs or devices as defined in section 201(g) and 201(h), respectively, of the [1938 act] or are a combination of drugs and devices.[8]

Although FDA had asserted authority over IVDs, when the agency issued its device establishment regulations, FDA exempted clinical laboratories from the registration requirements.[9] There is no suggestion in the preambles to the proposed or final establishment registration regulations that FDA intended to distinguish between clinical laboratories that used LDTs and those that used IVDs.[10] Indeed, the preamble to the final rule states "the Commissioner believes that full service laboratories and similar establishments are exempted from registration."[11]

FDA has long maintained that clinical laboratories that develop and perform LDTs are "acting as manufacturers of medical devices and are subject to FDA jurisdiction" under the FDCA.[12] FDA, however, also historically has acknowledged the importance of LDTs to patient care,[13] and therefore has exercised "enforcement discretion" with respect to most tests developed in-house by laboratories and not sold as "test kits,"[14] while purporting to reserve its right to develop LDT-specific requirements in the future.[15]

More recently, FDA has expressed concerns about the potential risks to patients if LDTs are not properly validated, including risk of missed diagnosis, wrong diagnosis or failure to receive appropriate treatment.[16] FDA's concern has been heightened by the growing complexity of LDTs and the increasingly important role that diagnostic tests are playing in clinical decision making and disease management.[17] Additionally, because of the potential for testing to improve the safety and effectiveness of drugs, FDA has expressed concern that the tests used to inform drug selection and dosing be properly validated, and appears to consider FDA review a necessary component of ensuring such adequate validation.[18]

On July 19 and 20, 2010, FDA held a public meeting to discuss the agency's oversight of LDTs.[19] The *Federal Register* notice announcing the meeting stated that, because of the agency's public health concerns regarding LDTs, the agency "believes it is time to reconsider its policy of enforcement discretion over LDTs" and to adopt a "risk-based application of oversight" to LDTs.[20] The notice stated FDA's desire to receive stakeholder input as it develops a "draft oversight framework,"[21] and indicated that the agency planned to issue a draft framework for public comment "as soon as possible."[22]

At the meeting, FDA officials discussed the types of regulatory requirements that FDA was considering for LDTs, including establishment registration and device listing.[23] FDA officials also indicated that the framework would include premarket review for some LDTs and that FDA would prioritize review of "highest risk" tests.[24]

FDA officials stated that the LDT framework would be implemented through one or more guidance documents.[25] During the meeting, the Director of FDA's Center for Devices and Radiological Health (CDRH) was asked whether the agency planned to engage in rulemaking to implement new requirements for LDTs.[26] He responded:

> The reason why not for notice and comment rulemaking is because the requirements actually already apply now. The law is in effect. We have simply, as a matter of policy, determined not to exercise or not to enforce that authority as of right now. So when we engage in enforcement discretion, either put it in place or take it back, that is a guidance process. It is a matter of policy. It is not imposing a new requirement. The requirements are already there.[27]

More recently, at a June 27, 2011, meeting regarding the reauthorization of MDUFA, FDA officials reiterated that FDA envisions a "risk-based, phased-in approach" toward LDTs, and will issue "three guidance documents coming out together that will detail the proposed road forward in oversight of laboratory developed tests."[28] According to the officials, one guidance will address the "overall framework," the second will discuss "the means by which FDA will gather information on what LDTs are being offered," and the third will "help laboratories understand the differences and similarities between CLIA regulations and the Quality System Regulations (QSRs)."[29] This article assumes that one of these guidances will include a registration and listing requirement for at least some clinical laboratories.

IV. RESEARCH AND RESPONSE

To proceed in accordance with the APA, FDA should take three actions. Each of these actions is discussed in this section.

A. Discontinue the guidance development process regarding oversight of LTDs.

Guidance documents cannot, as a matter of law, "create or confer any rights for or on any person."[30] Further, according to FDA's own regulations, guidance documents "do not establish legally enforceable rights or responsibilities" or "legally bind the public or FDA."[31] In the past, FDA took the position that guidances constituted the "formal position of FDA," but that position was overturned by *Community Nutrition Institute v. Young*.[32]

Subsequently, Congress amended the FDCA to clarify that FDA must promulgate rules—not issue guidance documents—in order to create legally enforceable requirements.[33] FDA's good guidance practices regulations now make clear that guidance documents "describe the agency's interpretation of or policy on a regulatory issue," but are not binding on either FDA or the public.[34]

The Supreme Court has long held that interpretive rules, such as guidance documents, must be consistent with the regulation they purport to interpret.[35] If an agency seeks to amend a legislative rule, such as a regulation issued through proper notice-and-comment procedures, the agency must do so by issuing another legislative rule.[36]

If FDA were to issue a guidance document purporting to require clinical laboratories to register as device establishments, the guidance would conflict with the express language of 21 C.F.R. § 807.65(i), which specifically exempts clinical laboratories from device establishment registration. Because section 807.65(i) is part of FDA's device establishment regulations, which were issued through the notice-and-comment rulemaking process, the regulations are "legislative rules." In order to revoke this exemption and to require clinical laboratories to begin registering as device establishments, under longstanding precedent, FDA would need to amend the device establishment registration regulations through notice-and-comment rulemaking.[37]

FDA could potentially argue that a guidance in which FDA interprets its regulations to require clinical laboratories to register would not contravene section 807.65(i), because that exemption language was not meant to encompass *all* clinical laboratories but only those "whose primary responsibility to the ultimate consumer is to dispense or provide a service through the use of a previously manufactured device."[38] FDA could argue that clinical laboratories that develop LDTs are not using a "previously marketed device" and therefore were not intended to be included in the exemption.

This argument can be rejected on numerous grounds. First, at the time it issued the device establishment registration regulations in Part 807, FDA had already implemented regulations for and asserted authority over IVDs, and there is there is nothing in the preambles to the proposed or final regulations creating Part 807 that suggests that FDA intended to distinguish between clinical laboratories that used LDTs and clinical laboratories that used IVDs. Instead, as mentioned, FDA simply stated in the preamble to the final rule that "the Commissioner believes that full service laboratories and similar establishments are exempted from registration."[39]

Second, even clinical laboratories that develop LDTs typically use "previously manufactured" devices—*e.g.,* general purpose reagents, analyte specific reagents (ASRs), chemistry analyzers, and many other FDA-classified clinical laboratory-specific devices—in the course of providing laboratory testing services. Indeed, in the preamble to the proposed ASR regulations, FDA referred to ASRs as the "active ingredients" of LDTs developed by clinical laboratories, and the agency stated that it was regulating ASRs as a way of regulating the LDTs developed by clinical laboratories.[40]

Therefore, if FDA attempted to change its interpretation of the regulation to exempt from registration and listing only laboratories that do not use LDTs, the new interpretation would appear to conflict with the plain language of the regulation.

Section 510(k) of the FDCA, 21 U.S.C. § 360(k), expressly relies upon device establishment registration as the "trigger" for requiring the submission of premarket notification submissions. Specifically, section 510(k) provides that "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" must submit a premarket notification submission to FDA at least 90 days before making that introduction or delivery for introduction.[41]

Consistent with that statutory mandate, FDA's regulations provide that "each person *who is required to register his establishment pursuant to § 807.20* must submit a premarket notification submission to the Food and Drug Administration at least 90 days before he proposes to begin the introduction or delivery for introduction into interstate commerce for commercial distribution of a device intended use which meets any of the [specified] criteria."[42] Because, as discussed *supra,* clinical laboratories are currently exempt from device establishment registration, under the plain language of the FDCA and FDA's implementing regulations, FDA could not legally require clinical laboratories to submit 510(k) premarket notification submissions for their LDTs.

Thus, both the FDCA and implementing regulations link the 510(k) requirement to establishment registration. The logical negative inference from these provisions is that persons who are *not* required to register are also *not* within the universe of persons who may be required to submit 510(k) premarket notification submissions. Furthermore, since the link between registration and 510(k) submission is statutory, FDA could not simply amend section 807.87 to remove the need for registration as a prerequisite 510(k) submission. Indeed, it is axiomatic that an agency may not enact regulations that conflict with the agency's enabling statute.[43] Nor could FDA simply reinterpret section 807.87 as inapplicable when a laboratory acts as a manufacturer, because the link between registration and 510(k) submission is statutory in origin, thus the new interpretation would be in conflict with existing law. Therefore, the only way for FDA to impose 510(k) premarket notification requirements is to first amend section 807.65(i) through notice-and-comment rulemaking to remove the registration exemption for clinical laboratories.[44]

B. Engage in rulemaking to depart from longstanding agency practice in the regulation of LDTs.

Under the APA, an agency must engage in notice-and-comment rulemaking in order to substantively alter a regulatory regime.[45] The D.C. Circuit's holding in *Syncor International Corp. v. Shalala*[46] is particularly apposite here. In that case, the court held unlawful FDA's use of guidance to regulate as drugs positron emission tomography (PET) radiopharmaceuticals after more than a decade of enforcement discretion by the agency. Similar to its history with LDTs, FDA had "made a careful, considered decision not to exercise the full extent of its regulatory authority," but subsequently changed course based on changes in both technology and medical practice. According to the court, "[t]he reasons FDA has advanced for its rule—advancement in PET technology, the expansion of procedures in which PET is used, and the unique nature of PET radiopharmaceuticals—are exactly the sorts of changes in fact and circumstance which notice and comment rulemaking is meant to inform."[47]

Although CDRH representatives assert that the comprehensive regulation of LDTs would not "impos[e] a new requirement" on the industry,[48] it has been FDA's policy "since the implementation of the Medical Device Amendments of 1976" to exercise "enforcement discretion" and not "actively regulate" most LDTs.[49] Thus, as LDTs have developed over the past generation, they have generally not been subject to the statutory and regulatory requirements for medical devices, including device establishment registration.

Regulating clinical laboratories that develop LDTs as device manufacturers, and imposing medical device requirements on LDTs, would constitute a radical departure from FDA's longstanding approach. Moreover, FDA's rationale for this sweeping change—that "LDTs are becoming more complex, [and] diagnostic tests are playing an increasingly important role in clinical decisionmaking and disease management, particularly in the context of personalized medicine"—is "exactly the sort of change in fact and circumstance which notice and comment rulemaking is meant to inform."[50]

C. Engage with stakeholders throughout the process to understand the impact of FDA regulation on the continued development and availability of validated laboratory tests.

In its quest to develop an oversight framework for LDTs, FDA should be guided by past precedent, specifically its regulation of human tissue and cellular-based products. That initiative similarly involved FDA's development of a new regulatory framework for a novel, complex, rapidly developing, and not-previously-FDA-regulated technology at the intersection between medical product and medical practice. In that instance, FDA's approach was deliberate, incremental and transparent.[51] Spanning about a decade, it began with the publication of a "concept paper" identifying the "principal public health concerns and attendant regulatory issues" associated with the use of cellular and tissue-based products, and describing in broad terms a tiered, risk-based regulatory system.[52] The publication was followed by numerous, separate, meetings between high-level agency officials and a wide range of stakeholders, including professional accrediting bodies.[53] Only after such engagement did FDA then publish several separate notices of proposed rulemaking,[54] which ultimately culminated in regulations codified at 21 C.F.R Part 1271.[55]

FDA should, in developing an LDT regulatory framework, similarly follow a process that is deliberate, incremental and transparent, and that is informed by the clinical laboratories that the agency seeks to regulate as well as the users and beneficiaries of their services, namely, healthcare providers and patients. Notice-and-comment rulemaking—and not non-binding guidance—is the most effective way for FDA to accomplish its objectives, and under these circumstances is the only way for the agency to do so consistent with the APA.

V. IMPACT OF POLICY RECOMMENDATIONS

Notice-and-comment rulemaking is a bedrock principle of administrative law.[56] For regulated entities, rulemaking ensures transparency, fairness and the opportunity to apprise regulators of the potential unanticipated consequences of a regulatory proposal.[57] For administrative agencies, rulemaking ensures that they have the benefit of feedback from those they seek to regulate, lends credibility to agency decisions—particularly on controversial topics with far-reaching impact—and protects agencies from subsequent legal challenge.[58] Indeed, while properly promulgated regulations are entitled to significant judicial deference,[59] such deference is vastly reduced when an agency has failed to follow proper administrative procedure.[60]

Regulating LDTs would represent a substantial change in the regulatory universe for clinical laboratories. Not only would FDA be subjecting entirely new entities to regulation as "manufacturers" of medical devices, but the agency would also be imposing an entirely new regulatory framework on their tests. Even if clinical laboratories may, from a statutory perspective, be regulated as "manufacturers," their manufacturing processes are substantially different from other regulated entities, which will require FDA to resolve a significant number of technical and practical issues not present for other product categories. Furthermore, healthcare providers historically have relied on LDT-based laboratory tests in providing clinical care, and it will therefore be imperative to ensure that any new regulatory framework does not interfere with continued development of and access to LDTs.

VI. CONCLUSION

Although, as mentioned, there are numerous policy arguments that have been raised both for and against FDA regulation of LDTs, as a procedural matter, FDA must proceed through rulemaking in order to require registration and listing by laboratories that develop and perform LDTs. FDA's device establishment regulations have for the past 34 years exempted all clinical laboratories from establishment registration.[61] Because this policy was implemented through notice-and-comment rulemaking, under settled administrative law principles, FDA may change that policy only through the same mechanism. Further, because the FDCA and FDA regulations limit the requirement for premarket notification submissions to those required to register, FDA would be unable to require premarket notification submissions for LDTs without first amending its establishment registration regulations—through notice-and-comment rulemaking—to remove the exemption for clinical laboratories.

Rulemaking is also required for a separate, independent reason. Imposing registration, listing and premarket notification requirements on LDTs would constitute a significant departure from the agency's longstanding policy of enforcement discretion and would have significant financial and practical implications for clinical laboratories, as well as downstream implications for healthcare providers and patients who depend on the results of such tests in healthcare decision-making. Under settled case law, a policy shift of such magnitude can be effected only through notice-and-comment rulemaking.

SOURCES

1 *See* Gail Javitt, *In Search of a Coherent Framework: Options for FDA Oversight of Genetic Tests*, 62 Food & Drug L.J. 617, 622-23 (2007).

2 *See id.* at 624.

3 *See* GeneTests, www.genetests.org (last visited July 18, 2011).

4 *See* Medical Device Amendments of 1976 (MDA), Pub. L. No. 94-295, 90 Stat. 539 (1976). Prior to the enactment of the MDA, FDA was given only limited authority over medical devices by the Federal Food, Drug, and Cosmetic Act of 1938. *See* Pub. L. No. 75-717, chs. II, III, V, 52 Stat. 1040, 1040-46, 1049-52 (1938). The 1938 act, for example, did not give FDA authority to impose premarket review requirements on products regulated as devices. FDA nonetheless asserted that some articles meeting the definition of a "device" could be regulated as drugs and therefore subjected to the act's premarket review requirements for such products. This approach was sanctioned by the Supreme Court in 1969, when it upheld FDA's imposition of the 1938 act's premarket review requirements for drugs on "a laboratory aid known as an antibiotic sensitivity disc, used as a screening test for help in determining the proper antibiotic drug to administer to patients." United States v. An Article of Drug… Bacto-Unidisk, 394 U.S. 784, 784-85 (1969).

Following *Bacto-Unidisk*, FDA arguably could have required premarket approval for all IVD products by regulating them as drugs. Instead, the agency promulgated regulations that imposed detailed labeling requirements for all IVDs and preserved the agency's option of requiring premarket review only "when necessary." See 38 Fed. Reg. 7096, 7096 (Mar. 15, 1973). Consistent with this approach, FDA subsequently required premarket approval for IVDs marketed for diagnosis of gonorrhea and cancer. *See 38 Fed. Reg. 10,488 (Apr. 27, 1973); 39 Fed. Reg. 3705 (Jan. 29, 1974)*. This approach was successfully challenged, however, when FDA attempted to regulate an at-home pregnancy test kit as a drug, thereby requiring premarket review for the kit. United States v. An Article of Drug…

OVA II, 414 F. Supp. 660 (D.N.J. 1975). The court rejected FDA's attempt in relevant part because the term "drug," like the term "device," was defined as an article intended to diagnose "disease," and pregnancy "is not of itself a disease." *Id.* at 661.

5 *See generally* 21 U.S.C. § 360c(a)(1).

6 21 U.S.C. § 321(h).

7 42 Fed. Reg. 42,520 (Aug. 23, 1977).

8 *See* 38 Fed. Reg. 7096, 7096 (Mar. 15, 1973) (codified as amended at 21 C.F.R. § 809.3(a)). Following the enactment of the MDA, FDA amended its IVD regulations to remove any reference to such products being subject to regulation as drugs. *See* 45 Fed. Reg. 7474, 7484 (Feb. 1, 1980). Unlike IVDs, FDA has never defined the term "laboratory-developed test" in its regulations. The agency, however, has described LDTs in various contexts. In one *Federal Register* notice, FDA described LDTs as "tests that are developed in-house by clinical laboratories." *See* 62 Fed. Reg. 62,243, 62,249 (Nov. 21, 1997). Similarly, in a draft guidance, FDA has asserted "LDTs are tests that are developed by a single clinical laboratory for use only in that laboratory." FDA, Draft Guidance for Industry, Clinical Laboratories, and FDA Staff: In Vitro Diagnostic Multivariate Index Assays (July 26, 2007).

9 *See* 42 Fed. Reg. at 42,528 (codified at 21 C.F.R. § 807.65(i)).

10 *See generally* 42 Fed. Reg. 45,520; 41 Fed. Reg. 37,458 (Sept. 3, 1976).

11 42 Fed. Reg. at 42,522.

12 62 Fed. Reg. 62,243, 62,249 (Nov. 21, 1997).

13 *Id.* ("FDA recognizes that the use of in-house developed tests has contributed to enhanced standards of medical care in many circumstances….").

14 *But c.f.* FDA, Draft Guidance for Industry, Clinical Laboratories, and FDA Staff: In Vitro Diagnostic Multivariate Index Assays (July 26, 2007) (stating FDA's view that algorithm-based LDTs are not subject to enforcement discretion); 65 Fed. Reg. 18,230, 18,231, 18,234 (Apr. 7, 2000) (codified at 21 C.F.R. § 809.40) (providing requirements for the labeling and testing of samples collected by using over-the-counter test sample collection systems for drugs of abuse testing); Warning Letter from Steven I. Gutman, M.D., M.B.A., Director, Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD), CDRH to David P. King, President & CEO, Laboratory Corporation of America (Sept. 29, 2008) (concluding that the OvaSure™ test used by LabCorp that was "designed, developed, and validated by investigators at Yale University and not LabCorp" was "not within the scope of laboratory developed tests over which the agency has traditionally exercised enforcement discretion"); *see also* Untitled Letter from James Woods, Deputy Director, Patient Safety and Product Quality, OIVD, CDRH, to James Plante, Founder and CEO, Pathway Genomics Corp. (May 10, 2010) (stating that genetic test developer's product was subject to regulation as a device in part because the test sample collection kits were distributed directly to consumers); Untitled Letter from Alberto Gutierrez, OIVD, CDRH, to deCODE Genetics (June 10, 2010) (same); Untitled Letter from Alberto Gutierrez, OIVD, CDRH, to 23andMe, Inc. (June 10, 2010) (same); Untitled Letter from Alberto Gutierrez, OIVD, CDRH, to Navigenics (June 10, 2010) (same).

15 62 Fed. Reg. at 62,252 (noting that, "if future developments in laboratory technologies or marketing of in-house developed tests indicate that additional regulation is necessary to provide an appropriate level of consumer protection, FDA may reevaluate whether additional controls over in-house developed tests are warranted.").

16 75 Fed. Reg. 34,463, 34,463 (June 7, 2010).

17 *Id.*

18 *See, e.g.,* FDA, Draft Guidance for Industry and Food and Drug Administrative Staff: In Vitro Companion Diagnostic Devices (July 14, 2011).

19 75 Fed. Reg. at 34,463.

20 *Id.* at 34464.

21 *Id.*

22 *Id.*

23 Transcript, FDA Public Meeting on Oversight of Laboratory Developed Tests 75 (July 19, 2010) (statement of Liz Mansfield) ("We will probably need a list of who offers what. We don't know what the universe of LDTs is now. They are not registered and listed with us, and nobody has these records, or at least they are not telling us…. [W] e will probably need to expand our registration and listing in order to encompass all the tests that are out there."), *available at* http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM226203.pdf.

24 *Id.* at 75-77.

25 *Id.* at 77.

26 *Id.* at 82.

27 *Id.*

28 *See* FDA, Minutes from Negotiation Meeting on MDUFA III Reauthorization, June 27, 2011, *available at* http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/ucm263026.htm.

29 *Id.*

30 21 U.S.C. § 371(h)(1)(A).

31 21 C.F.R. § 10.115(d)(1).

32 818 F.2d 943 (D.C. Cir. 1987); *see also* 44 Fed. Reg. 22,323, 22,335 (Apr. 13, 1979) (calling "into question FDA's procedure for issuing advisory opinions and guidelines that purport[ed] to bind the agency and thereby constrain the agency's discretion").

33 *See* Food and Drug Administration Modernization Act of 1997 (FDAMA), Pub. L. No. 150-115, § 405, 111 Stat. 2296, 2368 (1997); *see also* Gen. Elec. Co. v. EPA, 290 F.3d 377, 382-83 (D.C. Cir. 2002) (document identified as a "guidance" is a legislative rule because it purports to bind regulated entities and the agency).

34 *See* 21 C.F.R. §§ 10.115(b)(1), (d)(1).

35 *See, e.g.,* Bowles v. Seminole Rock and Sand Co., 325 U.S. 410, 414 (1945) (holding that an administrative interpretation carries controlling weight "unless it is…inconsistent with the regulation"); see *also* Hemp Industries v. DEA, 333 F.3d 1082 (9th Cir. 2003) (invalidating an interpretive rule issued by DEA that sought to ban the sale of all products containing naturally occurring THC, the active ingredient in marijuana, on the ground that the interpretive rule conflicted with DEA's regulations, and DEA had failed to follow notice and comment procedures in issuing the interpretive rule).

36 *See* Shalala v. Guernsey Memorial Hospital, 514 U.S. 87, 100 (1995) (holding that APA rulemaking would be required if the Medicare Provider Reimbursement Manual § 233 issued by HHS adopted a new position inconsistent with any of the Secretary's existing regulations); National Family Planning & Reproductive Health Ass'n v. Sullivan, 979 F.2d, 227, 235 (D.C. Cir. 1992) (quoting as a "maxim of administrative law" the principle that, "if a second rule repudiates or is irreconcilable with a [prior legislative rule], the second rule must be an amendment of the first; and of course an amendment to a legislative rule must itself be legislative").

37 *See, e.g., Guernsey Memorial Hospital*, 514 U.S. at 100.

38 *See* 21 C.F.R. § 807.65(i).

39 42 Fed. Reg. at 42,522.

40 *See* 61 Fed. Reg. 10,484, 10,484 (Mar. 14, 1996).

41 *See* 21 U.S.C. § 360(k) (emphasis added).

42 21 C.F.R. § 807.87(a) (emphasis added).

43 *See* 5 U.S.C. § 706(2)(A) ("The reviewing court shall…hold unlawful and set aside agency action, findings, and conclusions found to be arbitrary, capricious, an abuse of discretion, *or otherwise not in accordance with law*…") (emphasis added); Citizens to Preserve Overton Park, Inc. v. Volpe, 401 U.S. 402, 413-14 (1971) ("In all cases agency action must be set aside if the action was 'arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law' or if the action failed to meet statutory, procedural, or constitutional requirements.") (citation omitted).

44 In contrast to premarket notification, the FDCA does not limit the requirement to submit a premarket approval (PMA) application to persons required to register. *See* 21 U.S.C. § 360c(f)(1); 21 C.F.R. pt. 814. Thus, in theory, FDA could require a clinical laboratory to submit a premarket approval application (PMA) for that LDT even if the clinical laboratory could not be required to register. This type of one-size-fits all approach to LDT regulation, however, would be inconsistent with the "risk-based application of oversight" to LDTs the agency has said it will follow, 75 Fed. Reg. at 34,464; *see also* July 19, 2010, LDT Meeting Tr. at 75-76, and it would also be inconsistent with the classification-based system created for medical devices by the MDA, 21 U.S.C. § 360c(a)(1). It would, moreover, be illogical for FDA to require PMAs for LDTs for which the agency would be precluded from requiring 510(k) premarket notification submissions, and that are developed and performed by entities that FDA cannot legally require to register.

45 *See* United States Telecom Ass'n v. FCC, 400 F.3d 29, 35 (D.C. Cir. 2005) ("[F]idelity to the rulemaking requirements of the APA bars courts from permitting agencies to avoid those requirements by calling a substantive regulatory change an interpretive rule."); Appalachian Power Co. v. EPA, 208 F.3d 1015, 1024 (D.C. Cir. 2000) (a guidance document establishing a new regulatory regime constitutes a legislative rule for which notice-and-comment rulemaking is required); Alaska Prof. Hunters Ass'n, Inc. v. FAA, 177 F.3d 1030, 1034-35 (D.C. Cir. 1999) (holding FAA could not impose new requirements on hunters after more than 30 years of non-enforcement without providing opportunity to comment through rulemaking).

46 Syncor Int'l Corp. v. Shalala, 127 F.3d 90, 95 (D.C. Cir. 1997).

47 *Id.*

48 *See* July 19, 2010, LDT Meeting Tr. at 82.

49 *See* 75 Fed. Reg. 34,463, 34,463 (June 17, 2010).

50 *Syncor Int'l Corp.,* 127 F.3d at 95. We recognize that the Supreme Court has long affirmed an agency's right to change its policies so long as the agency supplies a "reasoned analysis for the change." See Motor Vehicle Mfr.'s Ass'n v. State Farm Mut. Auto. Ins., 463 U.S. 29, 42 (1983). An agency, however, may not change its policies in a way that "simply disregard[s] rules that are still on the books." *See* FCC v. Fox Television Stations, Inc., 129 S. Ct. 1800, 1811 (2009). As discussed, because of the existing FDA regulation exempting clinical laboratories from establishment registration, FDA may not simply change its policy and require such laboratories to register without first amending the regulation through the usual notice-and-comment procedures.

51 *See generally* Richard Merrill, *Human Tissue and Reproductive Cloning: New Technologies Challenge FDA*, 3 Houston J. Health L. & Pol'y 1 (2002).

52 *See* FDA, Proposed Approach to Regulation of Cellular and Tissue-Based Products 9 (Feb. 1997).

53 *See, e.g.*, 60 Fed. Reg. 36,808 (July 18, 1995) (workshop regarding MAS cells); 60 Fed. Reg. 58,088 (Nov. 24, 1995) (workshop regarding cord blood stem cells); 61 Fed. Reg. 4786 (Feb. 8, 1996) (workshop regarding peripheral blood stem cells); 61 Fed. Reg. 9185 (Mar. 17, 1996) (Commissioner's roundtable regarding MAS cells).

54 *See, e.g.,* 63 Fed. Reg. 26,744 (May 14, 1998) (proposed rule regarding establishment registration and listing); 66 Fed. Reg. 1508 (Jan. 8, 2001) (proposed rule regarding current good manufacturing practices (cGMPs)).

55 *See* 66 Fed. Reg. 5447 (Jan. 19, 2001) (final rule regarding establishment registration and listing); 69 Fed. Reg. 29,786 (May 25, 2004) (final rule regarding cGMPs).

56 *See* 5 U.S.C. § 553.

57 *See, e.g.,* Richard J. Pierce, Jr., *Two Problems in Administrative Law: Political Polarity on the District of Columbia Circuit and Judicial Deterrence of Agency Rulemaking*, 1988 Duke L.J. 300, 308-09; Alan Morrison, *The Administrative Procedure Act: A Living and Responsive Law*, 72 Va. L. Rev. 253, 256-58 (1986).

58 *See, e.g.,* Richard A. Merrill, *FDA and the Effects of Substantive Rules*, 35 Food Drug Cosmetic L.J. 270, 279-80 (1980).

59 Chevron U.S.A., Inc. v. Natural Resources Defense Council, Inc., 467 U.S. 837 (1984).

60 United States v. Mead Corp., 533 U.S. 318 (2001).

61 *See* 21 C.F.R. § 807.65(i), *see also* 42 Fed. Reg. at 42,528.

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