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Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD 20852

Re: Citizen Petition Regarding FDA Regulation of Laboratory Developed Tests

CITIZEN PETITION

A. ACTION REQUESTED

The Washington Legal Foundation (WLF) submits this petition under 10 C.F.R. § 10.30 to request that the Commissioner of Food and Drugs determine that the U.S. Food and Drug Administration (FDA) will not regulate as medical devices any assays developed by clinical laboratories strictly for their in-house use (so-called "home brew" assays or "laboratory developed tests"). The substantive legal basis for making this request is consistent with that set out in a Citizen Petition on the same subject submitted October 22, 1992 and denied by the Agency six years later (August 12, 1998).[1] However, the facts and law driving the conclusion that these laboratory developed tests are not subject to regulation as devices are much more clear in 2006 than at the time of the earlier petition. In addition, because of FDA's recent enforcement actions and a newly issued draft guidance document, there is now an urgent need for FDA to comply with the Administrative Procedure Act (APA).

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[1] See Citizen Petition, FDA Docket 1992P-0405, submitted by Hyman, Phelps & McNamara, P.C. (Oct. 22, 1992). That petition requested *inter alia*:

> "[T]hat the Commissioner of Food and Drugs not regulate as medical devices assays developed by clinical reference laboratories strictly for in-house use; . . . [that no FDA Compliance Policy Guide (CPG)] assert that FDA has the authority to regulate 'home brew' assays, even if the CPG also disclaims any intent to exercise this alleged authority."

This petition is not intended as a direct response to FDA's September 7, 2006 draft guidance regarding certain assays employed by clinical laboratories.[2] Therefore, this petition does not address the substance of that draft guidance, although WLF notes that the draft guidance contains significant ambiguities and is extraordinarily broad in its reach.

Additionally, this petition does not address the recent report by the U.S. Government Accountability Office (GAO) on nutragenetic testing.[3] The tests that were the subject of the GAO's investigation are sold directly to consumers, and the biological samples analyzed for such tests are collected by consumers in their homes. The laboratory developed tests that are at issue in this petition are not sold directly to consumers. Rather, the laboratory developed tests covered by this petition are ordered for a patient by a licensed health care practitioner, with the results reported directly to that health care practitioner.

B. INTERESTS OF PETITIONER

WLF is a public interest law and policy center with supporters in all 50 states. WLF devotes a substantial portion of its resources to defending and promoting free enterprise, individual rights, and a limited and accountable government. WLF has been involved in numerous government proceedings relating to FDA regulation. For example, WLF successfully challenged the constitutionality of FDA restrictions on speech regarding off-label uses of FDA-approved products.[4] In addition to working to ensure that FDA regulation does not exceed constitutional and statutory limits, WLF regularly

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[2] *See,* FDA, Center for Devices and Radiological Health, Office of In Vitro Diagnostic Device Evaluation and Safety, *Draft Guidance for Industry, Clinical Laboratories, and FDA Staff: In Vitro Diagnostic Multivariate Index Assays* (hereinafter "IVDMIA Draft Guidance") (Sept. 7, 2006), available at http://www.fda.gov/cdhr/oivd/guidance/1610.pdf.

[3] *Nutragenetic Testing: Tests Purchased from Four Web Sites Mislead Consumers*, Hearing Before the S. Special Comm. on Aging, 109th Cong. (2006) (Statement of Gregory Kutz, Managing Director, Forensic Audits and Special Investigations, GAO).

[4] *Washington Legal Found. v. Friedman*, 13 F. Supp. 2d 51 (D.D.C. 1998), *appeal dism'd*, 202 F.3d 331 (D.C. Cir. 2000).

monitors FDA to ensure that the agency complies fully with procedural rules governing administrative action.[5]

C. STATEMENT OF GROUNDS

Background

Although the general grounds for making this request are consistent with those set out in the 1992 petition, both the facts and the law have changed materially in the years since the 1992 petition was denied. For many years, FDA asserted that it could regulate laboratory developed tests as "unapproved medical devices," but it did not act on that assertion of jurisdiction and explicitly acknowledged that such assays were "exempted" from regulation. Very recently, however, FDA has begun taking action against individual clinical laboratories offering laboratory developed tests, seeking to regulate them as medical devices. Additionally, FDA stated in a recent draft guidance document that some laboratory developed tests constitute "test systems" that are subject to FDA authority as Class II or Class III medical devices.[6] The Agency says that it is now identifying particular laboratory developed tests that it intends to exclude from the category of laboratory tests over which FDA, based on a claimed exercise of its discretion, has declined to date to exercise enforcement authority.[7]

Prior to the release of the September 7, 2006 IVDMIA Draft Guidance, a number of laboratories reported that FDA told them that their in-house tests were medical devices and that they must comply with the Federal Food, Drug, and Cosmetic Act (FFDCA) or stop offering their tests. Moreover, WLF has been advised that prior to the release of the IVDMIA Draft Guidance, over two dozen laboratories were asked by FDA to contact the Agency to discuss their in-house tests. The reason provided by FDA for such discussions was that the Agency believed that these tests were or might be "unapproved" devices.

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[5] *See, e.g.*, Citizen Petition dated August 7, 2006 (requesting FDA to cease use of Warning Letters to announce new substantive policies regarding drug promotion).

[6] *See*, FDA, IVDMIA Draft Guidance, *supra* note 2, at 3-4.

[7] *Id.* at 3.

Thus, in a short period, FDA has gone from taking no regulatory action against laboratories for offering these tests to clinicians, to determining that some such tests are subject to device regulatory requirements.

In addition, FDA is requiring other laboratories to describe their services because, according to the Agency, those services raise device regulatory issues. These recent FDA actions have forced many clinical laboratories to meet with FDA or otherwise devote significant resources to interactions with the Agency. Laboratory developed tests have suddenly gone from being unregulated by FDA to regularly being subjected to FDA scrutiny, review, and regulation. FDA is asserting that state-licensed and Clinical Laboratory Improvement Amendments (CLIA)-certified clinical laboratories that offer in-house assays are subject to FDA's jurisdiction as "manufacturers" of medical devices and that it has jurisdiction to regulate these assays as new and "unapproved" medical devices. Further, FDA is threatening to take action unless the laboratories agree to comply with FDA's device requirements, *e.g.*, treating the tests as investigational devices, or seeking premarket clearance/approval. These threats have been conveyed to numerous laboratories within the past few months.

These events constitute company-specific enforcement action – taken without promulgating or following any kind of public standards for determining when, whether, and how a laboratory developed test would qualify to be regulated as a medical device. FDA's actions against specific entities, as well as the content of its IVDMIA Draft Guidance, reflect policy making that is inconsistent with the FFDCA; and even if that policy making were statutorily authorized, it violates the APA's requirement that substantive rules be adopted only after compliance with notice-and-comment rulemaking procedures.

The Importance of Laboratory Developed Tests. Laboratory developed tests play an essential role in health care delivery. For example, FDA has cleared or approved only a few molecular diagnostic tests, yet well over a thousand different tests are being used every day by clinicians to better inform diagnostic and therapeutic decisions. When new infectious agents first appear and a new diagnostic test is urgently needed for patient

care, it is generally a laboratory developed test, not an FDA-approved or cleared device, that first meets that medical need. For patients with cancer, laboratory developed tests have entered wide clinical use in helping to manage their care. It is recognized in the medical community and by FDA that such laboratory developed tests play an indispensable and critical part in the health care system.

Adverse Consequences of FDA Regulation. It is equally well understood that imposition of a requirement that these tests – and future laboratory developed tests – go through the FDA's premarket review process and comply with FDA's device regulatory rules would have a crippling effect on the ability of clinical laboratories to continue to provide access to these tests. Laboratories are not operated as medical device manufacturers. Although they must meet the demanding standards for compliance with CLIA, they do not maintain the procedures and documents for compliance with FDA Quality System Regulation (QSR).[8] Nonetheless, in the IVDMIA Draft Guidance, FDA is asserting that some laboratory developed tests are, in fact, subject to QSRs, as well as to the Medical Device Reporting (MDR) (adverse event reporting) regulation.[9] When specific guidance has been requested as to what a laboratory must do to meet the QSR regulations with respect to laboratory developed tests, FDA reportedly has responded by saying that its QSR rules are widely disseminated and that it is the laboratory's responsibility to figure out for itself how procedures developed for medical device manufacturers would apply to clinical laboratories.

Brand new compliance procedures and documentation would need to be created for clinical laboratories to meet this new FDA regulatory regime. For the thousands of in-house assays already being offered by laboratories, retrospectively developing design history files, as required by the QSR at 21 C.F.R. § 820.30(j), would be well-nigh impossible. The imposition of medical device reporting, promotional restrictions, limits on laboratory test modifications, and other FDA regulatory requirements would all cause

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[8] 21 C.F.R. Part 820.

[9] 21 C.F.R. Part 803; *see* FDA, IVDMIA Draft Guidance, *supra* note 2, at 5.

dramatic changes in the way laboratories operate – and preclude the offering of many tests altogether.

Laboratories constantly innovate and improve their tests; the need to comply with FDA's regulations would prevent many of these changes form being made, and severely inhibit the flexibility of laboratories and their ability to meet clinicians' needs, *e.g.*, identifying rapidly changing pathogens such as SARS and HIV.

FDA's actions have immediate and serious consequences. For laboratories offering their in-house developed tests to clinicians, those ramifications go well beyond the obvious, like loss of private investment capital or loss in stock value where a company involved is traded publicly. Another important adverse consequence is the effect on third-party coverage of and payment for these assays. When FDA compels an in-house assay to be labeled "investigational" while awaiting clearance or approval,[10] that "investigational" status typically triggers automatic denial of coverage for the assay under health benefit plans. This loss of coverage extends to those insured under public (Medicare and Medicaid) programs as well as those insured by private payers.[11]

That commonly used laboratory developed tests will now be deemed "investigational" by FDA is not mere speculation. FDA has asserted that some

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[10] *See* IVDMIA Draft Guidance, *supra* note 2, at 4-5.

[11] Typical of the health benefit plan language denying coverage of "investigational" clinical laboratory services, and setting forth the criteria that must be fulfilled to regain coverage, is language found in health benefit plans offered by The Regence Group (Blue Cross/Blue Shield plans that cover Idaho, Oregon, Utah and Washington):

> In this manual, the term "investigational" means that the medical technology does not meet The Regence Group's technology assessment criteria, as defined below. If any one or more of the criteria are not met, the technology will be determined to be investigational [non-covered as never "medically necessary" for any patient's care] . . . : 1. The technology [device] must have final approval from the Food and Drug Administration (FDA) for those specific indications and methods of use that The Regence Group is evaluating. Any approval that is granted as an interim step (i.e. Treatment IND) or for humanitarian purposes (i.e., HDE) in the FDA regulatory process is not sufficient.

Medical Policy, available at http://www.regence.com/trgmedpol/intro/.

Although Medicare rules allow coverage for devices subject to an Investigational Device Exemption (IDE), claims submission is substantially more cumbersome for IDE devices than for items or services that are not subject to an IDE, and coverage is not assured even when these procedures are followed.

laboratory developed tests now widely used by clinicians and covered by insurance payers must be labeled in accordance with the Agency's "Investigational Use Only" (IUO) regulations and comply with regulations governing investigational products, including the human subject investigations requirement.[12] This "investigational" status imposed by FDA seriously disadvantages physicians and patients that previously had access to an assay as a covered and "medically necessary" clinical laboratory service under many health benefit plans. This "investigational" status imposed by FDA means that insureds now either have no access to these assays (test results) or have access only if they can afford to pay the full price of the services (often thousands of dollars for typical genetic home brew assays). The adverse consequences for hundreds of thousands of citizens (and their families) who can get a needed service *only* if it is covered by their health insurance are materially different than (and were not raised in) the 1992 Citizen Petition.[13]

The adverse consequences for physicians and patients who rely on laboratory developed tests – because there are no FDA-cleared tests available – to select among treatment options (especially with cancer diagnoses) provide ample health-related justification for FDA ceasing efforts to enforce compliance with FFDCA medical device requirements by targeting individual clinical laboratories performing these assays. There are millions of individuals who are directly affected by FDA's recent reversal of its decision to exempt "home brew" assays from medical device regulations – and thus would benefit from being provided an opportunity to understand fully what FDA is doing or asserting it has the jurisdiction to do, to evaluate FDA's explanation of the lawfulness and reasonableness of its actions, and to provide comments on what the impact will be on their lives and their families' lives. These interested parties also should have the opportunity to make recommendations as to what, if any, additional regulatory oversight

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[12] IVDMIA Draft Guidance, *supra* note 2, at 4-5 (citing 21 C.F.R. §§ 809.10(c)(2)(ii), 812.3).

[13] Even if a payer agrees to cover the assay, it will only provide coverage for those patients enrolled in an IDE trial, which will generally have a limit on the number of patients who may be tested and which may have narrow inclusion criteria.

should be required for laboratory developed tests, and under which Agency and which statutory framework such oversight should proceed, *before* FDA acts to regulate these assays. Satisfying those interests will entail FDA compliance with notice-and-comment rulemaking, as mandated by the APA.

Legal Analysis

WLF has concluded that FDA has acted unlawfully in asserting jurisdiction over laboratory developed tests and the entities performing these assays. That conclusion is based on three grounds. First, Congress has assigned responsibility for regulating clinical laboratory services to the Centers for Medicare and Medicaid Services (CMS), not to FDA. It did not give FDA the authority to regulate laboratory developed tests. Second, if there were any ambiguity regarding which branch of the Department of Health and Human Services (HHS) is authorized to regulate clinical laboratory services, the Secretary of HHS resolved that ambiguity by authorizing issuance of CLIA regulations that assign that responsibility to CMS. Third, even if FDA has some authority to regulate clinical laboratory services, it has gone about it in the wrong way. FDA has announced a new regulatory policy by sending letters to individual laboratories, and by issuing a draft guidance document, rather than following the notice-and-comment procedures mandated by the APA.

First: Congress Assigned Responsibility Elsewhere. Congress did not assign responsibility for regulating clinical laboratory services and their in-house developed (home brew) assays to FDA under the FFDCA, but to CMS under CLIA, with its comprehensive implementing regulations in 1992 and 2003.[14] FDA has wrongly concluded that it has jurisdiction over all CLIA-regulated tests.

CMS has been assigned by Congress the exclusive responsibility to regulate "high complexity" "methods developed in-house" (CLIA nomenclature for "home brew"). This assignment of responsibility in lieu of FDA medical device regulation is longstanding and widely understood; indeed, only one commenter, out of more than

[14] Clinical Laboratory Improvements Act of 1988 (CLIA), Pub. L. No. 100-578 (1988); 57 Fed. Reg. 7002 (Feb. 28, 1992); 68 Fed. Reg. 64,350 (Nov. 13, 2003).

6,000 comments submitted on CLIA rulemaking, appeared not to know (or accept) the prevailing regulatory scheme. Only one commenter "disagreed with the [CLIA] requirement to establish performance specifications for those methods developed in-house, [cleared by the FDA, but] modified by the laboratory, ***or not cleared by FDA***" for purposes of meeting the CLIA quality oversight requirements and, thereby, being lawfully marketed.[15]

On the other hand, the 1976 Medical Device Amendments (MDA) – under which FDA claims regulatory authority – did not refer to laboratories at all. Nothing in that legislation even suggested that laboratory developed tests were now suddenly medical devices subject to the FFDCA. WLF is aware of nothing in the legislative history suggesting that the MDA was intended to grant FDA such jurisdiction, and WLF is equally unaware of any evidence that at the time of the MDA's passage FDA itself suggested that laboratory tests needed to comply with the FFDCA (as amended by the MDA).

Conversely, the 1988 CLIA legislation was directed specifically at laboratories. The authority for regulating laboratories – including tests developed in-house – was conferred exclusively on what is now CMS. Passed by Congress in 1988, CLIA established quality standards for virtually all clinical laboratory testing. On February 28, 1992, the CLIA regulations that set forth "all requirements applicable to clinical laboratories engaged in testing in interstate commerce" were codified.[16] The final regulations established "uniform requirements" to ensure the quality of laboratory services.[17]

CMS has the authority to regulate essentially all laboratory testing through CLIA. Under an interagency agreement, the Centers for Disease Control and Prevention (CDC) was given the responsibility for assisting CMS with scientific and technical issues. FDA

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[15] 68 Fed. Reg. 3640, 3655 (Jan. 24, 2003) (emphasis added).

[16] 57 Fed. Reg. 7002.

[17] 68 Fed. Reg. 3640.

was delegated the authority to implement some of CLIA's complexity categorization provisions.[18] FDA does not have the authority to regulate clinical laboratory services and their in-house developed (home brew) assays in any other manner. Indeed, FDA is mentioned several times in the preamble to the 2003 CLIA final rule, yet there is no acknowledgment or reference to any authority of FDA to regulate laboratory developed tests.[19] If all laboratory developed tests were subject to FDA's approval or clearance requirements, presumably this would have been mentioned in the 62-page preamble.

Courts also look to "common sense" considerations in determining what law applies in a given case. Here is the common sense analysis in this situation: clinical laboratories that develop, validate, and offer to physicians their "home brew" assays are not medical device manufacturers. They are, as CLIA states, "***a facility for the*** biological, microbiological . . .pathological, or other ***examination of materials*** derived from the human body ***for the purpose of providing information*** for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings."[20] They are regulated by CMS under its CLIA regulations, not by FDA under the FFDCA.

The "high complexity" assays lawfully offered by these laboratories under their state licenses and CLIA certificates (tests *not* regulated by the FDA as re-stated in the Preamble to the 2003 CLIA rule[21]) match FDA's longstanding definition of "home brew" exempt from its device regulations:

> [Laboratories using] general purpose reagents and general purpose instruments . . . to set up an in-house ("home brew") test or laboratory testing service. While specimens . . . travel to the lab setting up this service, ***the test itself is not marketed outside of the single lab setting up this service.*** * * * Although not

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[18] 68 Fed. Reg. 64350.

[19] 68 Fed. Reg. 3640.

[20] 42 U.S.C. § 263(a) (emphasis added).

[21] 68 Fed. Reg. 3640.

> part of the [analyte specific reagent] rule, ***FDA has indicated that . . . FDA is not requiring the in-house test to go through premarket FDA review***.[22]

Note that FDA published this clarifying statement – explaining that FDA does *not* regulate "home brew" tests – only a month after CMS issued its comprehensive new quality oversight standards on January 24, 2003.

Notwithstanding this consistent, longstanding, and widely understood FDA policy not to regulate these assays as "unapproved medical devices," the Agency for the first time – fully 30 years after the passage of the MDA – is now both asserting that laboratory developed tests can be brought under FDA's jurisdiction and invoking that purported authority to act. Such an argument flies in the face of the explicit language of CLIA and its implementing regulations, which deal directly with laboratories – as compared to the FFDCA and its regulations, which do not address laboratory developed tests.

In each of the following scenarios, FDA now is asserting that it has regulatory jurisdiction: (1) when an *in vitro* diagnostic product manufacturer brings a new test to the FDA and it is cleared for sale to laboratories; (2) when a laboratory employs an FDA-cleared test, but modifies that test (whereby the test reverts to "high complexity" status under CLIA, making it "home brew" under FDA's logic); (3) when a laboratory develops and establishes an "in-house" method (home brew); and (4) when a laboratory uses established test methods but creates its own algorithm to interpret and utilize test results in decision-making for individual patients. In all four alternative routes to a laboratory offering a specific test method, FDA appears to be claiming authority to regulate the assay as a medical device. **And a clinical laboratory avoids regulation as a "manufacturer" of "unapproved medical devices" only by restricting its test menu to FDA-cleared test systems used exactly as stated in the FDA-cleared labeling. For example, an entity employing any decision aids in patient care that meet the three-part definition of an IVDMIA (*e.g.*, the Memorial Sloan Kettering Kattan nomogram for determining risk of recurrence of prostate cancer; or the**

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[22] FDA, Center for Devices and Radiological Health, Guidance for Industry, Analyte Specific Reagents; Small Entity Compliance Guide, 2-3 (Feb. 26, 2003) (emphasis added).

Nottingham Scale, available on the American Cancer Society website, for assessing prognosis with cancer patients) would be deemed a medical device manufacturer subject to compliance with FDA regulations promulgated under the FFDCA. Under this interpretation of FDA's authority, **every** academic medical center, large hospital, and reference laboratory in the country is operating in violation of the FFDCA – as are many physician practices – and they therefore are subject to enforcement action. This situation is clearly one that Congress neither contemplated nor intended.

In addition, this interpretation of FDA's authority to act under its statutes completely negates the regulatory structure of CLIA.[23] The Secretary of HHS would not have cleared the CLIA rule as published in January 2003 if he had determined that the longstanding FFDCA device provisions essentially would void huge parts of the new CLIA rules. Congress intended that CMS, through CLIA, regulate clinical laboratories, including the imposition of any premarket or post-market controls on the offering of in-house developed test methods (home brew). Now, FDA is improperly asserting jurisdiction over these CLIA-regulated in-house assays. When two statutes overlap

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[23] In reversing the FDA attempt to regulate tobacco as a "new drug" under the FFDCA, the U.S. Supreme Court clearly acknowledged the compelling public health problems that are attributable to tobacco use. It nonetheless ruled that these health concerns simply did not matter in determining whether FDA had jurisdiction over tobacco products under the FFDCA. The Court set some clear boundaries for FDA decision-making. Using language highly relevant to whether laboratory developed tests should be deemed "medical devices" under the FFDCA, the Court ruled that the words of a statute must be interpreted based on the context in which they appear:

> In determining whether Congress has specifically addressed the question at issue, a reviewing court should not confine itself to examining a particular statutory provision in isolation. The meaning – or ambiguity – of certain words or phrases may only become evident when placed in context. *Brown v. Gardner*, 513 U.S. 115, 118 (1994) ("Ambiguity is not a creature of definitional possibilities, but of statutory context."). ***It is a fundamental canon of statutory construction that the words of a statute must be read in their context and with a view to their place in the overall statutory scheme. . . . [T]he meaning of one statute may be affected by other Acts, particularly where Congress has spoken subsequently and more specifically to the topic at hand***.

FDA v. Brown & Williamson Tobacco Corp., 529 U.S. 120, 132-133 (2000) (emphasis added) (internal citations omitted). Congress has directed in CLIA that CMS shall regulate "home brew" assays, and CLIA – not the FFDCA – is the legislation dealing specifically with laboratory developed tests.

(here, CLIA and FFDCA), the specific statute closely applicable to the substance of the issue at hand (CLIA) controls over a more generalized provision (FFDCA).[24] [25]

Second: The Secretary of HHS Assigned Responsibility Elsewhere. If the statutory language at issue here is deemed ambiguous, then the Secretary of HHS has the authority to determine which agency within the Department should regulate laboratories. Put another way, the Secretary would be authorized to determine FDA's scope of authority in implementing the device-related provisions of the FFDCA, and to determine CMS's scope of authority in implementing CLIA regulations with clinical laboratories and clinical laboratory services, including a "test system" as defined in CLIA.[26] (Neither FDA nor CMS acting individually has the authority to decide the issue. Even a joint statement issued by program managers at FDA and CMS collectively would not be determinative. If the statutory language were truly ambiguous, only the Secretary – acting through lawful rulemaking – would have the authority to decide the issue.)

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[24] *Farmer v. Employment Sec. Comm'n of North Carolina*, 4 F.3d 1274, 1284 (4th Cir. 1993); *Radzanower v. Touche Ross & Co.*, 426 U.S. 148, 153 (1976) ("'Where there is no clear [congressional] intention otherwise, a specific statute will not be controlled or nullified by a general one, regardless of the priority of enactment.'") (quoting *Morton v. Mancari*, 417 U.S. 535, 550-51 (1974)).

[25] FDA's improper and unprecedented assertion of jurisdiction over laboratory developed tests in many ways parallels the Agency's attempt to establish jurisdiction over drugs compounded by pharmacies. Several decades after passage of the FFDCA, FDA claimed that all compounded drugs were unapproved new drugs, just as now FDA claims that all laboratory developed tests are medical devices subject to regulation under the FFDCA. A federal district court recently rejected FDA's efforts to extend its jurisdiction over pharmacies. *Med. Ctr. Pharmacy v. Gonzalez*, ___ F. Supp. 2d ___, 2006 U.S. Dist. LEXIS 65427 (W.D. Tex. Aug. 30, 2006). In rejecting FDA's position, the court stated, "If compounded drugs were required to undergo the new drug approval process, the result would be that patients needing individually tailored prescriptions would not be able to receive the necessary medication due to the cost and time associated with obtaining approval." *Id.* at *28-*29. Imposing FDA approval as a prerequisite for patients to receive individualized treatments based on new laboratory developed tests raises precisely the same public health concerns cited by Judge Junell in his decision rejecting FDA's efforts to eliminate pharmacy compounding capabilities.

[26] CLIA regulations define a "test system" as " [T]he instructions and all of the instrumentation, equipment, reagents, and supplies needed to perform an assay or examination and generate test results." 42 C.F.R. § 493.2. In its IVDMIA Draft Guidance, FDA uses the term "test system" in a way that completely overlaps this definition but states – without any explanation – that its regulatory definition "is not linked with use of the term in 42 C.F.R. Part 493." IVD Draft Guidance, *supra* note 2, at 3.

The Secretary has decided that between these two regulatory regimes, the authority resides with CMS. The Secretary would not have implemented the comprehensive 1992 CLIA rules after four years (1988-1992) of negotiating the parameters and limits of regulation with organized medicine, and would not later have implemented the 2003 CLIA rule, if he accepted the view that there are *no* laboratory tests out of FDA's reach, and if he agreed that the judgment about whether and what FDA should regulate is wholly at FDA's discretion. FDA authority to regulate "home brew" assays cannot be squared with the comprehensive regulation of tests systems under CLIA. There is no evidence that the Secretary – or anyone else – contemplated that CLIA's carefully constructed regulatory structure could be superseded by a simple FDA letter telling a laboratory that, pursuant to a new Agency policy, the laboratory's "home brew" assay would henceforth be subject to regulation as a device under the FFDCA.

CLIA regulations are comprehensive in scope, with detailed pre-analytic, analytic, and post-analytic requirements designed to ensure consistently high quality in all laboratory testing and reporting of reliable test results to treating clinicians.[27] A key component of CLIA regulations is the very high standard set for qualification of supervisors of "high complexity" laboratories, precisely those laboratories offering the "home brew" assays that are now under FDA scrutiny.[28]

Additionally, with comprehensive rules effective April 2003, CMS updated CLIA compliance requirements for record retention, proficiency testing, procedure manuals for all test systems at all locations of use, establishment or verification of performance specifications for every test system (specifications that depend on whether a system has been cleared by FDA), calibration and calibration verification procedures, quality control procedures, and ongoing quality assessment measures.[29] Imposing the obligation on clinical laboratories to comply with FDA's QSRs in addition to these extensive CLIA

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[27] 42 C.F.R. Part 493.

[28] 68 Fed. Reg. 6340.

[29] 42 C.F.R. Part 493.

quality oversight requirements for their laboratory developed assays would present huge, and possibly insurmountable, challenges for even the most highly skilled laboratory directors. If the Secretary had intended such burdensome and duplicative regulation, one would have expected a statement to that effect in regulations approved by the Secretary. Yet, even though FDA is mentioned in multiple places in the preamble to the 2003 CLIA rule, there is no mention made of adding layers of FDA regulation to every laboratory director's compliance burden.

Third: FDA Informal Policymaking Violates the APA. FDA and HHS must comply with the APA if they seek to change the agency's practices and established policies on "home brew" tests (and the regulation of laboratories that develop and offer such tests). Until recently, a well-established FDA policy provided that such assays were exempt from regulation and that the agency had no intent to regulate them. FDA cannot depart from that precedent without providing reasoned explanation for the change.[30]

Moreover, FDA must properly "open" these changes in policy to public comment and review so that all can fully appreciate what FDA is attempting to do. Under the APA, before FDA may begin imposing its new, ill-defined policy on a laboratory-by-laboratory basis, it must explain itself and open the new policy up to public comment. A draft guidance document, covering a fraction of laboratory developed tests -- the Agency's apparent preferred pathway to accomplishing this policy change -- is not adequate.

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[30] *Greyhound Corp. v. ICC*, 551 F.2d 414, 416 (D.C. Cir. 1977) ("[A]s this court noted in *Columbia Broadcasting System, Inc. v. F.C.C.*, . . . when an agency decides to reverse its course, it must provide an opinion or analysis indicating that the standard is being changed and not ignored, and assuring that it is faithful and not indifferent to the rule of law"); *International Union, United Auto Workers v. NLRB*, 459 F.2d 1329, 1341 (D.C. Cir. 1972) ("It is an elementary tenet of administrative law that an agency must either conform to its own precedents or explain its departure from them."); *Baltimore and Annapolis R.R. Co. v. Washington Metro. Area Transit Comm'n*, 642 F.2d 1365, 1366, 1370 (D.C. Cir. 1980) ("an agency cannot abandon a rule established by its precedent without first stating its reasons for doing so. . . . [I]t is vital that an agency justify a departure from its prior determinations.")

The APA requires notice-and-comment rulemaking whenever a federal agency wants to act in a way that materially changes established burdens and benefits,[31] "by which rights or obligations have been determined, or from which legal consequences will flow."[32] Clearly, FDA is now acting to substantively change the "rights and obligations" of owners of clinical laboratories. And the "legal consequences [that] will flow" from not meeting FDA's demands are well known, *e.g.*, a Warning Letter, seizure, injunction, civil penalties, or prosecution.

Case law establishes the process by which such "substantive" (versus purely non-binding or "interpretive") policies are to be promulgated . . . *before* they lawfully can be enforced. Until FDA sets out, through notice-and-comment rulemaking that engages all interested parties, a clear statement of the basis for its conclusions that it lawfully can regulate a clinical laboratory's in-house assays as a medical device and the manner in which it intends to implement that authority, any attempt to regulate these assays as medical devices (or clinical laboratories as "manufacturers" of medical devices) is legally impermissible.

As noted above, FDA has contacted many laboratories about the applicability of FDA regulations to their operations and assays.[33] FDA has also released a draft guidance document that asserts authority over particular laboratory developed tests. The criteria that FDA is employing, however, represent a change in a substantive rule, not a mere

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[31] APA notice-and-comment requirements achieve three purposes: "to ensure that agency regulations are tested by exposure to diverse public comment, to ensure fairness and an opportunity to be heard, and to enhance judicial review." *Bldg. Indus. Ass'n. of Superior Cal. v. Babbitt*, 979 F. Supp. 893, 901 (D.D.C. 1997). Without such open and public discussion of substantive proposed changes in its enforcement policies, FDA thwarts the overarching APA intent that "interested parties" shall be heard.

[32] *Bennett v. Spear*, 520 U.S. 154, 178 (1997) (internal quotations omitted).

[33] The initiation of inquiries – even if FDA ultimately decides that a particular "home brew" test is not a device – nonetheless imposes significant costs and uncertainties on the recipients and on companies that are targets of these FDA actions. The uncertainty created by FDA's sudden declaration of jurisdiction over laboratory developed tests also has had negative effects on the entire laboratory industry, and its wholesale assertion of jurisdiction (through issuance of the draft guidance document) will have even more profound negative effects.

policy shift. Therefore, proper rulemaking pursuant to the notice-and-comment provisions of the APA is required.

Conclusion

There is one inescapable conclusion to be reached: FDA needs to stop asserting or enforcing any policy that it has jurisdiction over laboratory developed or "home brew" tests and/or that it will regulate such assays as "unapproved medical devices." FDA cannot take what Congress has not granted. In the alternative, if FDA nonetheless determines that it does indeed have the authority to regulate these assays as medical devices and that it will exercise that authority, then that is a substantive, new policy that cannot lawfully be enforced until notice-and-comment rulemaking on that subject is completed.

FDA should not interfere with those who practice "laboratory medicine" in highly innovative and skilled labs around the country and who are regulated federally under CLIA as well as under state laboratory and medical practice acts. This is an essential part of the U.S. medical and public health infrastructure that cannot afford to be degraded, however inadvertently.

The new "bench to bedside to trench" reality spreading throughout medicine, largely as a result of mapping the human genome and applying the power of computing, requires a new dynamic for bringing what we have learned to improving patient care.[34]

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[34] Enriqueta Bond, Ph.D., then Chair of the Clinical Research Roundtable of the National Academy of Sciences/Institute of Medicine, recently spoke to the need to ensure that research breakthroughs translate into improved patient health care: "We need to knit this group of stakeholders together in a more seamless fashion to facilitate the translation of basic knowledge into things that work in people and then get it applied." Quoted in V. Elliott, *Translation Frustration: When Research Doesn't Reach*, AMNews (Nov. 1, 2004). No part of contemporary medicine comes closer to achieving that translational goal than laboratory medicine in its validation and offering of home brew assays, e.g., for those new (West Nile virus) or rapidly mutating (HIV or bird flu) infectious diseases and for cancers now treated, often with no change in outcome, with "shotgun" therapy regimens that many fear more than death itself. We see evidence of clinical breakthroughs on a regular basis. *See, e.g.*, Jennifer Levitz, *New Tests May Help Treat Lung Cancer*, WALL ST. J. (Aug. 10, 2006) at D4 (describing test that predicts which early-stage lung cancer patients are likely to suffer a recurrence, making them prime candidates for chemotherapy). *See also* Joyce O'Shaughnessy, M.D., *Molecular Signatures Predict Outcomes of Breast Cancer*, 355 NEW ENG. J. MED. 615, 615 (2006) (reporting a finding that suggests that "biology [the genetic make-up of a woman's individual tumor] trumps anatomy in the determination of prognosis and the benefit of chemotherapy.").

That is the essence of the contributions made by those who develop, validate, and offer to clinicians these essential in-house assays. Laboratory developed tests are an essential part of modern medicine.

FDA's attempt to regulate these clinical laboratory services goes beyond the scope of the FFDCA and is inconsistent with Congress's allocation of responsibility under the FFDCA and CLIA, as reflected in the 2003 CLIA regulations. FDA's new regulatory initiatives also violate the APA.

Accordingly, WLF requests that:

(1) The Agency immediately cease and desist seeking to regulate laboratory developed tests as medical devices because FDA does not have the legal authority to regulate these services; and

(2) If FDA continues to take the position that it has the legal authority to regulate laboratory developed tests as medical devices, the Agency must proceed with proper notice-and-comment rulemaking, as required under the APA.

D. ENVIRONMENTAL IMPACT

The action requested in this petition will have no impact on the environment.

E. ECONOMIC IMPACT

WLF will submit information upon request of the Commissioner. Petitioner believes that FDA's inappropriate assertion of regulatory authority over clinical laboratories is raising health care costs and having harmful economic impact on patients and their doctors. Conversely, granting this Petition, WLF believes, will result in the more effective use of available assays and therefore have a favorable economic impact.

A September 8, 2006 article in *Science* reported that scientists have identified nearly 200 genes that cause breast and colorectal cancers. *See* Jocelyn Kaiser, *First Pass at Cancer Genome Reveals Complex Landscape*, 313 SCIENCE 1370 (2006). In reference to the *Science* article, USA TODAY reported that Francis Collins, director of the National Human Genome Research Institute, said that doctors have noted that cancer is not one disease but hundreds of diseases, and that researchers have been moving away from "one size fits all" cancer treatments. Liz Szabo, *Killer Cancer Genes ID'd*, USA TODAY, Sept. 7, 2006.

F. CERTIFICATION

The undersigned certify that, to the best of the knowledge and belief of the undersigned, this Petition includes all information and views on which this Petition relies, and that it includes all representative data and information known to WLF which are unfavorable to the Petition.

_____
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Chairman and General Counsel

_____
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cc: Honorable Michael O. Leavitt, Sec'y of HHS
Honorable Andrew C. von Eschenbach, Comm'r, Food & Drug Administration
Sheldon Bradshaw, Chief Counsel, Food & Drug Administration