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Re: Docket # 2006P-0402; Washington Legal Foundation Citizen Petition;
Comments of Hyman, Phelps & McNamara, P.C. in Support of Petition

Hyman, Phelps & McNamara, P.C. (“HPM”) submits these comments in support of the Washington Legal Foundation (“WLF”) Citizen Petition dated September 28, 2006, requesting the Food and Drug Administration (“FDA”) to determine that it will not regulate as medical devices any assays developed by clinical laboratories strictly for in-house use, also known as “home brew” or “laboratory developed tests” (“LDTs”). Like WLF, HPM is concerned by the Agency’s shift in regulatory approach toward LDTs as reflected in letters issued to clinical laboratories offering LDT-based services, and by FDA’s publication of the Draft Guidance for Industry, Clinical Laboratories, and FDA Staff: In Vitro Diagnostic

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Multivariate Index Assays (Sept. 7, 2006) (“IVDMIA Draft Guidance”).¹ HPM believes such actions are not authorized by the Federal Food, Drug, and Cosmetic Act (“FDCA”) or the Clinical Laboratory Improvement Amendments of 1988 (“CLIA ‘88”). Moreover, FDA’s approach represents a fundamental change in regulatory requirements. Even if this reversal were within the Agency’s statutory authority, FDA’s mechanism is procedurally and substantively lacking under the Administrative Procedure Act (“APA”). We submit, therefore, that the WLF petition should be granted. While we support federal efforts to strengthen and improve the regulation of LDTs, we do not believe that the IVDMIA Draft Guidance meets the applicable legal standards.

I. Congress Has Not Given FDA Authority To Regulate Clinical Laboratories Or The Testing Services Offered By Clinical Laboratories, Including LDTs

The theory on which FDA claims jurisdiction over LDTs is that LDTs are “devices” within the FDCA definition.² As WLF notes in its Petition, however, the 1976 Medical

¹ HPM represents laboratories that would be subject to regulation under the IVDMIA Draft Guidance, other laboratories offering LDTs, and companies that are considering offering LDTs, some of which may be subject to regulation as IVDMIAAs.

² In the IVDMIA Draft Guidance, FDA asserts that because an IVDMIA is a “test system that employs data, derived in part from one or more in vitro assays, and an algorithm that usually, but not necessarily, runs on software, to generate a result that diagnoses a disease or condition or is used in the cure, mitigation, treatment, or prevention of disease,” it is “therefore a device within the meaning of the Act.” IVDMIA Draft Guidance at 1-2. This approach conflicts with CLIA ‘88, which defines a “clinical laboratory” as an entity whose purpose is to examine human specimens and “provid[e] information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings.” 42 U.S.C. § 263a(a). The IVDMIA Draft Guidance does not attempt to reconcile the broad FDCA definition of “device” with the specific CLIA definition that already covers the laboratory’s operations.

Device Amendments (“MDA”) to the FDCA – through which FDA acquired most of its current authority to regulate medical devices – say nothing about FDA regulation of clinical laboratories or about the diagnostic testing services such laboratories provide. This is hardly surprising considering that nine years prior to the enactment of the MDA and its revised “device” definition, Congress had already assigned regulatory authority over clinical laboratories and services to the Public Health Service (“PHS”) under the Clinical Laboratories Improvement Act of 1967 (“CLIA ‘67”).

Until the establishment of the Health Care Financing Administration (“HCFA”) in 1977, the PHS, through the Centers for Disease Control (“CDC”), was responsible for development and oversight of the CLIA ‘67 regulatory program.³ The CDC published regulations implementing CLIA ‘67 in 1968.⁴ HCFA, predecessor to the Centers for Medicare & Medicaid Services (“CMS”), acquired oversight of the CLIA ‘67 program in 1979 through an interagency agreement and memorandum of understanding with the CDC.⁵ The CDC retained responsibility to assist HCFA in obtaining technical and scientific expertise.⁶ FDA was given the role under CLIA ‘67 to provide technical advice on blood

³ See 53 Fed. Reg. 29,590, 29,590-91 (Aug. 5, 1988) (“Medicare, Medicaid and CLIA Programs; Revision of the Clinical Laboratory Regulations for the Medicare, Medicaid, and Clinical Laboratories Improvement Act of 1967 Programs; Proposed Rule”); 55 Fed. Reg. 9538, 9538-39 (Mar. 14, 1990) (“Medicare, Medicaid and CLIA Programs; Revision of the Laboratory Regulations for the Medicare, Medicaid, and Clinical Laboratories Improvement Act of 1967 Programs; Final Rule”).

⁴ See 33 Fed. Reg. 20,043 (Dec. 31, 1968).

⁵ See 53 Fed. Reg. at 29,591; 55 Fed. Reg. at 9539.

⁶ Id.

bank programs and blood products, and to give feedback to CDC/HCFA concerning the appropriateness of revisions to the CLIA regulations.⁷

In 1988, responding to public concerns about the deficiencies and limitations of CLIA '67, Congress enacted CLIA '88.⁸ Observing that “the nature of clinical laboratory testing ha[d] changed dramatically,” and that “today’s clinical laboratories would hardly be recognizable by the framers of the original CLIA,”⁹ the House Report explained that the purpose of CLIA '88 was to “strengthen federal oversight of clinical laboratories to assure that the tests results are accurate and reliable.”¹⁰ Despite congressional hearing testimony recognizing and praising the beneficial contributions of FDA in “influenc[ing] the quality of the instruments and materials available for laboratory testing,”¹¹ and in “oversight of the devices and other technical aspects of lab testing,”¹² Congress did not confer regulatory authority over clinical laboratories or their services to FDA. Nor, despite the extensive discussion of federal regulation of laboratories and the history of this regulation, did

⁷ 53 Fed. Reg. at 29,590-91; 55 Fed. Reg. at 9538-39.

⁸ Pub. L. No. 100-578, 102 Stat. 2903; 42 U.S.C. § 263a.

⁹ H. R. No. 100-889, at 11-12 (1988).

¹⁰ Id. at 8.

¹¹ Health Care Financing Administration’s Management of Medical Laboratories: Hearings before the Subcommittee on Oversight of Government Management of the S. Comm. on Governmental Affairs, 100th Cong. 280 (1988) (written testimony of Dr. Paul J. Wiesner, CDC Training and Laboratory Program Office Director).

¹² Clinical Laboratory Improvement Act: Hearing on H.R. 4325, H.R. 4927 and H.R. 4928 Before the Subcomm. on Health and the Environment of the H. Comm. on Energy and Commerce, 100th Cong. 77 (1988) (testimony of William L. Roper, HCFA Administrator).

Congress intimate that FDA had any role to play in regulating laboratories or their tests, even though Congress was aware that laboratories developed their own tests. Congress' discussion of FDA's role was limited to the Agency's review of medical devices sold in interstate commerce. If FDA had been given the authority to regulate laboratories, Congress could not have completely ignored such a key element of the regulatory framework. Yet nothing in CLIA '88 or in the legislative history indicates that Congress believed it had given FDA the authority to regulate LDTs. Instead, Congress expanded and enhanced the authority of HCFA (now CMS) to regulate laboratories. The 1988 legislation increased the number of laboratories subject to regulation by HCFA, and charged the Secretary of the Department of Health and Human Services (who delegated this authority to HCFA) with the establishment of a new and comprehensive regulatory scheme for oversight and certification of clinical laboratory testing procedures.

Within the regulatory framework promulgated to implement CLIA '88,¹³ FDA did acquire a tangential role in making test categorization determinations during its normal process of reviewing device marketing applications.¹⁴ Significantly, however, the CLIA regulations provide an alternative method of test categorization for "test systems, assays, or examinations not commercially available" – i.e., LDTs not reviewed by FDA. Specifically, categorization determinations for "not commercially available" assays and test systems are

¹³ See 42 C.F.R. Part 493.

¹⁴ See *id.* § 493.17(c)(1)(i). See also 68 Fed. Reg. 64,350 (Nov. 13, 2003) (Delegation of authority to FDA) ("Notice is hereby given that I have delegated to . . . [FDA] the authority . . . to implement CLIA's complexity categorization provisions. . . . The existing delegation of authority to the Administrator, [CMS] concerning CLIA is unaffected").

to be made by CDC.¹⁵ This alternative categorization method would be unnecessary if, as FDA claims, LDTs were subject to its jurisdiction and to all the requirements of the MDA. FDA's receipt of this limited, expressly delegated authority to determine the test categorization of commercially marketed products is at odds with FDA's claim that it also has jurisdiction over all LDTs. The preamble to the CLIA regulations is voluminous. Yet nothing in that document suggests that FDA has concurrent jurisdiction over LDTs as devices.

Assuming for the sake of argument that there is any overlap of authority between CLIA and the FDCA with regard to "not commercially available" LDT methodologies, federal case law requires that the more specifically tailored statute – in this case, CLIA – be given precedence over the more general statute – here, the FDCA definition of "device."¹⁶ CLIA establishes a comprehensive, multifaceted regulatory framework specifically designed to regulate clinical laboratories. In contrast, the FDCA contains a single, broadly-worded definition of "device" that applies to a vast array of products. 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."¹⁷ An LDT or test system that "provid[es] information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings," within the CLIA '88

¹⁵ 42 C.F.R. § 493(c)(2) (emphasis added).

¹⁶ See, e.g., Radzanower v. Touche Ross & Co., 426 U.S. 148, 153 (1976); Morton v. Mancari, 417 U.S. 535, 550-51 (1974); Stewart v. Smith, 673 F.2d 485, 492 (D.C. Cir. 1982).

¹⁷ Davis v. Mich. Dep't of Treasury, 489 U.S. 803, 809 (1989).

definition of a “clinical laboratory” simply is not a “device” subject to FDA regulation under the MDA.¹⁸

The MDA was enacted to ensure more effective regulation of medical devices. Regarding the need for this legislation, the House Report noted: “[t]he regulatory authority provided the Food and Drug Administration by the 1938 Act . . . is limited to action after a medical device has been offered for introduction into interstate commerce and only when the device is deemed to be ‘adulterated’ or ‘misbranded.’”¹⁹ Moreover, the focus of the MDA – even with regard to diagnostic devices – was on marketed products sold to third parties for use in diagnosis:

¹⁸ FDA is not permitted to expand its jurisdiction beyond the authority granted in the FDCA. See, e.g., FDA v. Brown & Williamson Tobacco Corp., 529 U.S. 120, 161 (2000) (rejecting FDA’s attempt to regulate tobacco products on the theory that they were drug-delivery devices); Med. Ctr. Pharmacy v. Gonzales, 451 F. Supp. 2d 854, 858 (W.D. Tex. 2006), appeal filed (5th Cir. 2006) (holding that pharmacy-compounded drugs are “implicitly exempt” from the FDCA “new drug” definition). In Medical Center Pharmacy, FDA adopted an argument much like the one here, i.e., the term “new drug” covered all compounded drugs. This expansive “plain language” argument, which disregarded the legislative intent and structure of the FDCA, was rejected by the district court. See also, Brown-Forman Distillers Corp. v. Mathews, 435 F. Supp. 5 (W.D. Ky. 1976). In Brown-Forman, FDA claimed it had authority to require ingredient labeling on alcoholic beverages because they were a subcategory of “food.” The court concluded that Congress did not intend to give that jurisdiction to FDA, but to the Bureau of Alcohol, Tobacco and Firearms under the more specifically-tailored Federal Alcohol Administration Act (FAAA). Id. at 7. It also noted that for more than 35 years, FDA had not taken any steps to regulate alcoholic beverage labeling. Id. at 16. The court ruled that FDA’s attempt to regulate beverage ingredient labeling was invalid. Id. at 17.

¹⁹ H. R. No. 94-853, at 6 (1976).

The phenomenal increase in the availability of diagnostic products is responsible for the millions of tests performed daily

. . .

There are different types of hazards and deficiencies associated with different types of devices. Devices such as radiographic units which produce ionizing radiation, implanted devices such as pacemakers or hip prostheses, diagnostic devices such as electrocardiographs, and clinical laboratory apparatus such as autoanalyzers all present very different kinds of problems associated with design, manufacture, quality control, marketing, purchasing, use, maintenance, and repair.

Mr. President, the present legislative authority as expressed in the [FDCA] is clearly inadequate and this legislation is long overdue.²⁰

There is no mention of the test methods or services developed and used in-house by laboratories, only a reference to products sold to laboratories, i.e., autoanalyzers. Nothing in the language of the MDA itself, or its legislative history, stated or implied that LDTs fell into this new grant of authority.

LDTs were not novel in 1976. Laboratories had been creating their own tests for decades. FDA's theory of jurisdiction over LDTs would mean that in 1976, Congress both imposed regulation of laboratories on top of CLIA '67 without acknowledging that it had done so, and rendered all existing LDTs illegal without mentioning that either. It is inconceivable that Congress intended to delegate such significant regulatory powers to

²⁰ 121 Cong. Rec. 56143 (daily ed. Apr. 12, 1975) (statement of Sen. Schweiker).

FDA without expressly saying so.²¹ It is equally implausible that if FDA already had the authority to regulate LDTs in 1988, that Congress would have ignored this overlapping jurisdiction in enacting CLIA '88. FDA's assertion of jurisdiction over LDTs, which rests solely on a broad reaching of the definition of "device," cannot be reconciled with the structure of the MDA, its legislative history, or Congress' legislation directed specifically to laboratories in CLIA '67 and CLIA '88.²²

II. FDA's Departure From The Longstanding Practice Of Not Regulating LDTs Requires Notice-and-Comment Rulemaking

A. FDA's Consistent Policy For Thirty Years Since Enactment of the MDA Has Been Not To Regulate LDTs

Even if FDA had the authority to regulate LDTs, its longstanding policy, relied upon by industry, has been that FDA would not regulate LDTs. This policy cannot be reversed through an informal guidance document.

In January 1996, FDA convened a meeting of the Immunology Devices Panel to discuss the proposed device classification of analyte specific reagents ("ASRs"). The

²¹ See, e.g., Brown & Williamson, 529 U.S. at 160 ("Congress could not have intended to delegate a decision . . . [regarding regulation of tobacco products] to an agency in so cryptic a fashion."). See also Whitman v. Am. Trucking Assn's, 531 U.S. 457, 468 (2001) (Congress "does not, one might say, hide elephants in mouseholes.").

²² In 1992, HPM filed a citizen petition questioning FDA's assertion that LDTs could be regulated as devices. FDA Docket No. 92P-0405, CP1. Six years later, FDA rejected the petition. FDA Docket No 92P-0405, PDN1. FDA's response, however, did not adequately address the issues relating to jurisdiction and authority, and, in any event, is not dispositive of WLF's petition.

Director of FDA's Center for Devices and Radiological Health ("CDRH"), Dr. Bruce Burlington, stated in opening remarks:

We are in our twentieth year since the Device Amendments were passed and . . . we all understand that, in the world of in vitro diagnosis a great many products and a great many services simply are in the marketplace, are offered, in fact, often as the standard of care, and have not gone through the FDA premarket review system.²³

The CDRH Director of Clinical Laboratory Devices, Dr. Steven Gutman, explained during the same meeting:

There is a . . . category of test commercialization, which is not specifically described in the Code of Federal Regulations . . . in-house tests or so-called "home brew" tests. These assays have been a standard in laboratory medicine for decades, and they represent a heterogeneous group.

. . .
Tests developed as in-house tests are considered by the FDA to be medical devices potentially subject to pre-market review. Because of resource constraints and because of the existence of an on-site review program for these assays under CLIA '88, FDA has only rarely exercised regulatory authority in this area. . . .

FDA believes that there may be hundreds or perhaps thousands of "home brew" tests being performed probably at hundreds of academic medical centers, commercial laboratories and in other laboratory settings.

²³

FDA Immunology Devices Panel, Classification: Analyte Specific Reagents, 9-10 (Jan. 22, 1996) (statement of Dr. Bruce Burlington).

The current policy is directed at trying not to disrupt this mechanism for test production. We believe that in-house assays do represent a valuable mechanism for providing health care professionals with test results.²⁴

At the end of this panel meeting, Dr. Gutman acknowledged: “The truth of the matter is that we have a policy that does exist now not to regulate the ‘home brew’ market. Whether you accept this policy or not, I don’t think we are going to rush back and start regulating ‘home brew’ tests.”²⁵

In November of 1997, FDA promulgated the ASR classification regulation. With regard to LDTs, the preamble to this rule stated:

FDA believes that clinical laboratories that develop such tests are acting as manufacturers of medical devices and are subject to FDA jurisdiction under the act. However, FDA recognizes that the use of in-house developed tests has contributed to enhanced standards of medical care in many circumstances and that significant regulatory changes in this area could have negative effects on the public health. For these reasons, FDA declines to accept the suggestion that all in-house developed tests be classified as class II or III medical devices. FDA views this final rule as a reasonable regulatory step at this time. . . .²⁶

As the foregoing statements show, FDA’s unequivocal position and practice regarding LDTs from the time the MDA was enacted through publication of the ASR rule was not to regulate them. The Agency’s hands-off approach to LDTs persisted through the

²⁴ Id. at 20-22.

²⁵ Id. at 190.

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

next decade as evidenced by additional FDA public statements. For example, at the 2003 Secretary's Advisory Committee on Genetics, Health, and Society ("SACGHS"), the Director of CDRH, Dr. David Feigal, explained:

In-house tests is a well-established practice with a long history and regulated by CLIA The analyte-specific reagents that I mentioned earlier . . . are the building blocks or the active ingredients for many types of in-house tests. The ASR rules and the supervision of manufacturers of reagents was designed to allow for in-house tests with incremental control based on the tests.²⁷

At the same meeting, responding to a question about FDA's jurisdiction to regulate LDTs, Dr. Feigal indicated that the Agency had not definitively determined whether it had such authority:

Dr. Collins: Obviously, there has been an ongoing debate, it seems, about whether or not FDA has the legal authority to take a larger role in terms of their oversight of in-house testing of home brews. Earlier conclusions four or five years ago seemed to indicate that yes, the law would in fact cover that kind of authority if FDA chose to exercise it. More recently we understood there was a review of that going on, and I don't think there was ever a clear answer provided as to whether FDA currently feels they have that authority or not, not getting into whether FDA wants to use it right now, but does the FDA actually have that authority.

Is there anything new to say about the status of that legal review?

²⁷ HHS SACGHS, Second Meeting, 38 (Oct. 22, 2003) (hereinafter "2003 SACGHS Meeting Tr.") (statement of Dr. David Feigal).

Dr. Feigal: No. It's an issue that hasn't been settled.²⁸

During a July 2005 Immunology Devices Panel meeting concerning the Nymox Neural Thread Protein Kit, Dr. Gutman confirmed the Agency's hands-off policy for LDTs, suggesting that in the event of non-approval, the Nymox test could still be marketed "in-house":

There actually are two mechanisms for laboratory tests to enter the U.S. marketplace. One mechanism is for a sponsor to make a commercial kit or system, and then to sell it at multiple sites. . . .

There is, however, an alternative mechanism to enter the marketplace. Individual labs do have the opportunity to create what are called in-house or home-brewed tests, or laboratory testing services. There is actually regulation for those. That is under CLIA. It's a very different regulatory construct than FDA. That would be an operation at a single site so that you couldn't export the test to multiple sites, although you would be allowed to obtain samples from multiple sites. So samples can flow to the lab. . . . The company, as I understand it, and they can comment if I've got this wrong, is a CLIA certified lab and so it is permitted to market at this current time. . . . The FDA approval would allow them to export that product to other labs for use at other sites.²⁹

Thus, FDA's longstanding policy – repeated publicly on many occasions – has been that LDTs are not regulated by FDA and provide “an alternative mechanism to enter the marketplace.”

²⁸ Id. at 50.

²⁹ FDA Immunology Devices Panel of the Medical Devices Advisory Committee, Nymox Urine Neural Thread Protein (NTP) Kit (P040010), 139-41 (July 15, 2005) (statement of Dr. Steven Gutman).

B. FDA's Abrupt Reversal of Position, As Announced by the IVDMIA Draft Guidance, Is A Substantive Rule Requiring Notice-and-Comment Rulemaking

On September 7, 2006, representing a major departure from its 30-year policy of not regulating LDTs, FDA published the IVDMIA Draft Guidance. The document purports to “address[] the definition and regulatory status,” and “premarket pathways and postmarket requirements” for a class of LDTs the Agency calls “IVDMIAAs,” and to “dispel . . . existing confusion and clarify [the Agency’s] approach to regulation of IVDMIAAs.”³⁰

Contrary to FDA’s characterization, there is no “confusion” or need for “clarification” with regard to the Agency’s 30-year practice. As shown above, FDA has made its longstanding practice of not regulating LDTs, and the reasons for that approach, quite clear. Clinical laboratories have long relied upon FDA’s repeatedly affirmed approach. Numerous laboratories have made decisions and invested significant sums of money based on the need to comply with CLIA and other laboratory-based requirements, not the MDA. HPM has worked directly with laboratories that relied on FDA’s long-standing position of not regulating LDTs when developing products and making long-term investments. In claiming the need to “clarify” this “policy,” FDA may be trying to position the IVDMIA Draft Guidance as an interpretive statement exempt from APA notice-and-comment rulemaking. It is not. The IVDMIA Draft Guidance does not simply clarify existing rules and obligations, but instead subjects a class of products to a comprehensive regulatory regime. Taking a class of services that had never been regulated and declaring that they now are devices is not a “clarification.”

³⁰ IVDMIA Draft Guidance at 1-2.

The APA requires that substantive or legislative rules having the force and effect of law be established through notice-and-comment rulemaking.³¹ “Interpretive rules” and “general statements of policy” which are not substantive or legislative are exempt from the rulemaking requirements.³² In seeking to establish a new definition and to declare the regulatory status, as well as the premarket and postmarket requirements for a class of previously and intentionally unregulated items, the IVDMIA Draft Guidance, we believe, cannot properly be categorized as an “interpretive policy statement” exempt from APA requirements. On the contrary, the clear effect of the IVDMIA Draft Guidance, if finalized, will be to significantly alter the rights and obligations of CLIA-regulated clinical laboratories that develop and offer what the Agency calls IVDMIAAs. This represents a significant change in the legal obligations of laboratories, since previously laboratories were not regulated under the FDCA. In particular, such laboratories will have to prepare and submit marketing applications for their in-house “IVDMIA” tests, conform to the Quality System Regulation, comply with medical device reporting requirements, and meet FDA’s labeling requirements, among other regulatory obligations. Laboratories will need to make significant changes to adapt to an entirely new regulatory scheme. The failure to comply with the FDCA can result in civil and criminal sanctions.

Simply because a document “is entitled ‘guidance’ by an agency does not mitigate the tone of the language that follows its title.”³³ Nor does boilerplate language claiming that the document “does not create or confer any rights” or “operate to bind FDA or the

³¹ 5 U.S.C. § 553(b).

³² Id. § 553(b)(3)(A).

³³ Bellarno Int’l v. FDA, 678 F. Supp. 410, 415 (E.D.N.Y. 1988).

public.”³⁴ By altering the legal expectations and consequences for laboratories that offer LDTs in the nature of “IVDMIAAs,” the IVDMIA Draft Guidance is a substantive rule requiring notice-and-comment rulemaking.

The facts surrounding FDA’s publication of the IVDMIA Draft Guidance are similar to the situation reviewed by the court in Syncor Int’l Corp. v. Shalala.³⁵ In Syncor, the issue was the validity of an FDA guidance document purporting to regulate positron emission tomography radiopharmaceuticals (“PET drugs”) under the new drug provisions of the FDCA. A different FDA guideline issued ten years earlier had clarified that PET drugs would not be regulated. FDA argued that the new guidance was an interpretive policy statement since, in the absence of such guidance, the Agency could still choose to enforce the regulatory requirements against PET drug manufacturers. It contended that under the previous guideline, the applicable regulatory requirements had merely been “deferred.”

The court rejected FDA’s arguments noting that “enforcement discretion is relevant in determining whether an agency intended to bind itself, and therefore, in determining whether a pronouncement is a legislative rule or a general statement of policy.”³⁶ In

³⁴ See, e.g., Federal Farm Credit Banks Funding Corp. v. Farm Credit Admin., 731 F. Supp. 217 (E.D. Va. 1990) (where agency attempt to define standard established by authorities outside the agency has force and effect of substantive rule, court will look beyond agency’s characterization and require that notice-and-comment procedures be followed).

³⁵ 127 F.3d 90 (D.C. Cir. 1997).

³⁶ Id. at 96.

reaching its conclusion that the guidance was invalid for lack of notice-and-comment rulemaking, the court stated:

FDA made a careful, considered decision not to exercise the full extent of its regulatory authority – whatever that may be – over nuclear pharmacies in 1984. . . .

. . .

FDA does claim that PET technology has advanced and that PET has many more applications today than it did in 1984. And, after “[h]aving considered the available information,” FDA has concluded, by way of its challenged rule, that PET manufacturers “*should* be regulated.” 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. The 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.³⁷

In the IVDMIA Draft Guidance, FDA asserts “new development”-based reasons for its action which parallel the arguments rejected by the Syncor court:

FDA . . . has generally exercised enforcement discretion over laboratory-developed ASRs and laboratory-developed tests that use commercially available and laboratory-developed ASRs.

FDA took this approach because it believed it was regulating “the primary ingredients of most in-house developed tests,” and because it believed that laboratories certified as high complexity

³⁷

Id. at 95.

under [CLIA] “have demonstrated expertise and ability *to use ASRs* in test procedures and analyses.”

FDA believed it was regulating the primary ingredients of most in-house tests because it was regulating the common elements of in-house tests, including most ASRs, general purpose reagents, general purpose laboratory equipment, other laboratory instrumentation, and controls. IVDMIA include elements . . . that are not among these primary ingredients of in-house tests and that, therefore, raise safety and effectiveness concerns.

Also, as stated above, FDA decided to exclude laboratory-developed tests from the ASR rule due to its confidence in high-complexity laboratories’ ability to use ASRs. The manufacture of an IVDMIA involves steps that are not synonymous with the use of ASRs and that are not within the ordinary “expertise and ability” of laboratories that FDA referred to when it promulgated the ASR rule. Therefore, IVDMIA do not fall within the scope of laboratory-developed tests over which FDA has generally exercised enforcement discretion. IVDMIA must meet pre- and post-market device requirements under the Act and FDA regulations, including premarket review requirements in the case of class II and III devices.³⁸

The “new development” impetus for FDA’s IVDMIA Draft Guidance is further underscored by certain statements of Dr. Gutman concerning this document at the 2006 SACGHS meeting:

The multivariate guidance is a specific example of a guidance that is fueled by FDA’s concern that perhaps it wasn’t such a great idea not to regulate all laboratory-developed devices, and that perhaps the blanket application of enforcement discretion is

³⁸ IVDMIA Draft guidance at 2-3.

not a particularly brilliant public health move for all laboratory-developed devices.

...
[W]e were really worried about a growing category of tests that seemed to us not to fit [CLIA's] mold, not to be the kind of thinking an average inspector, whether working for CAP and COLA or CMS would be able to actually assess and understand. Tests had produced novelty with new safety and effectiveness concerns and tests that we thought were very poor fits for enforcement discretion.³⁹

As the Syncor court noted, this is precisely the kind of scenario that notice-and-comment rulemaking was intended to address.⁴⁰

³⁹ HHS SACGHS Eleventh Meeting (Nov. 13, 2006) (statement of Dr. Steven Gutman).

⁴⁰ FDA should recognize that notice-and-comment rulemaking is the appropriate pathway. In its eventual response to HPM's 1992 Citizen Petition objecting to language in a draft Compliance Policy Guide ("CPG") which suggested that FDA agency could regulate "home brew" tests used only in-house as medical devices, FDA explained:

At the time FDA received your citizen petition, FDA believed that it would respond to the petition after it considered the comments on the draft [CPG] and revised the draft. Upon further consideration of FDA's regulation of commercialized homebrew of other in vitro diagnostics and comments received, FDA believed it would be better to clarify some of the regulation of IVD issues through notice and comment rulemaking in the [ASR] rulemaking. FDA then published a revised draft of the [CPG] for public comment.

FDA response to Citizen Petition 92P-0405, at 1 (Aug. 12, 1998). FDA's response was correct: "it would be better to clarify" its approach to IVDMIA's through rulemaking.

FDA's attempt to affect its departure from settled practice through a guidance document sidesteps important issues that can only be addressed through notice-and-comment rulemaking under the APA. For example, had the Agency issued a proposed rule, it would have been required to compile and reference the applicable administrative record, and to address more thoroughly the statutory basis for its proposed action. It would also have needed to prepare an analysis discussing the significant additional costs expected to be incurred by affected clinical laboratories, and by patients as a result of increased regulation. One would further expect to see a discussion of the potential impact of the rule on innovation in light of the Agency's mandate to apply the least burdensome approach, and the critical importance of innovation to patient care.⁴¹ By including discussion of these important issues in a proposed rule, the Agency would be likely to receive a more diverse set of well-informed comments that more closely reflect the range of public concern and interest in this subject matter.⁴²

⁴¹ As Bill Gates recently noted, “[i]nnovation is the source of U.S. economic leadership and the foundation for our competitiveness in the global economy.” Bill Gates, Wash. Post, Feb. 25, 2007, at B7. See Elizabeth Lipp, Diagnosis, Prognosis, and Therapy Selection, Genetic Engineering News, Vol. 27, No. 3 (Feb. 1, 2007) (highlighting multiple new discoveries that could be affected by the IVDMA Draft Guidance.) An important element of fostering innovation is regulatory predictability. Changing long-established policies through this informal guidance document mechanism is inconsistent with predictability.

⁴² See NLRB v. Wyman-Gordon Co., 394 U.S. 759, 764 (1969) (notice-and-comment rulemaking provisions “were designed to assure fairness and mature consideration of rules of general application.”); Brown Express, Inc. v. United States, 607 F.2d 695, 701 (5th Cir. 1979) (“Congress realized that an agency’s judgment would be only as good as the information upon which it drew. It prescribed [the notice-and-comment] procedures to ensure that the broadest base of information would be provided to the agency by those most interested and perhaps best informed on the subject of the rulemaking at hand.”).

To take just one example of an issue requiring the kind of public discourse afforded only through the more formal APA rulemaking procedures, FDA's proffered definition of an IVDMIA – a test system “that employ[s] data, derived in part from one or more in vitro assays, and an algorithm that usually, but not necessarily, runs on software to generate a result that diagnoses a disease or condition or is used in the cure, mitigation, treatment, or prevention of disease,”⁴³ is vague. This description encompasses literally hundreds of LDTs currently in use by clinical laboratories. FDA has not provided any further distinguishing criteria or examples of specific tests that it believes do or do not fall within this broad category. That the Agency now realizes this is an issue is apparent from statements at the 2006 SACGHS meeting:

The IVDMIAs I think have been – this document has been overread, because while it's clearly a signal, it is a much narrower signal than I think the laboratory community or the community in general has appreciated. When we were thinking about the IVDMIAs that we were worried about and interested in, we were thinking about one dozen or two dozen products that might be percolating toward or on the market, and maybe this would be an incredible growth area in five or ten years. We weren't looking at dozens, hundreds or thousands of submissions. That never crossed our minds when we crafted this document. . . .

. . .

We were looking at a narrow niche of devices

What we clearly did not intend was that all algorithms would fall in this category. We never imagined that

⁴³ IVDMIA Draft Guidance at 3.

The device, just because it's multivariate, doesn't automatically mean it's an IVDMIA.⁴⁴

HPM is aware of approximately 200 tests on the market or under development that involve algorithms not yet widely known to the medical community and which, therefore, potentially could be considered IVDMIA's. Before embarking on this fundamental change in regulation of a subset of LDTs, FDA – and the public – would benefit from a full discussion of the impact, scope, and need. If, in fact, there are potentially hundreds of IVDMIA's that would need to be submitted over the next few years, presumably that would be very relevant to the Agency. These issues are best addressed through rulemaking, not guidance documents. If FDA intends to pursue its novel approach and regulate IVDMIA LDTs, believing it has the statutory authority to do so, it should withdraw the IVDMIA Draft Guidance and issue a proposed rule that provides the level of notice and explanation required by the APA.⁴⁵

Proceeding through rulemaking is also the appropriate mechanism for creating and classifying new devices. FDA has routinely used the classification process to define and identify classes of products which it wished to regulate, e.g., ASRs and

⁴⁴ 2006 SACGHS Meeting (statement of Dr. Steven Gutman). HPM appreciates these clarifying remarks about the intended scope of the IVDMIA definition. However, we believe the correct pathway to address these crucial definitional issues is through rulemaking.

⁴⁵ FDA's view that all LDTs are medical devices only makes it more critical that FDA follow proper procedural safeguards. Even if there were only "two dozen" IVDMIA's, FDA's use of a guidance document here establishes a precedent that could be used as a mechanism for reaching other subsets of the tens of thousands of different LDTs now on the market.

immunohistochemicals.⁴⁶ Establishing device classifications through rulemaking is routine and legally proper. The Agency has offered no explanation for failing to follow this process to create, in effect, a new product classification.

III. The Regulatory Shift Announced In The IVDMIA Draft Guidance, And Already Being Applied In Letters Issued to Clinical Laboratories, Is Arbitrary and Capricious

Agency action is arbitrary and capricious if:

the agency has relied on factors which Congress has not intended it to consider, entirely failed to consider an important aspect of the problem, offered an explanation for its decision that runs counter to the evidence before the agency, or is so implausible that it could not be ascribed to a difference in view or the product of agency expertise.⁴⁷

An agency “must examine the relevant data and articulate a satisfactory explanation for its action including a rational connection between the facts found and the choice made.”⁴⁸

Moreover,

when an agency reverses its course, a court must satisfy itself that the agency knows it is changing course, has given sound reasons for the change, and has shown that the rule is consistent with the law that gives the agency its authority to act. In addition, the agency must consider reasonably obvious alternatives and, if it rejects those alternatives, it must give

⁴⁶ See 21 C.F.R. § 864.4020; § 864.1860.

⁴⁷ Motor Vehicle Mfr’s Ass’n of the United States, Inc. v. State Farm Mut. Auto. Ins. Co., 463 U.S. 29, 43 (1983).

⁴⁸ Id.

reasons for the rejection [A]n agency is free to change course after weighing the competing statutory policies. But such a flip-flop must be accompanied by a reasoned explanation of why the new rule effectuates the statute as well as or better than the old rule.⁴⁹

FDA has not offered a thorough explanation for its reversal of policy on LDTs. At best, the IVDMIA Draft Guidance refers to the novel use of “elements” that are not among the traditional primary ingredients of in-house tests, and which “therefore, raise safety and effectiveness concerns,” and alludes to apprehension that the use of IVDMIAAs incorporating such elements is beyond the CLIA-regulated expertise and ability of clinical laboratories.⁵⁰ Whether that is true is open to debate. Because of the lack of a factual record – or any administrative record – FDA has provided no support for this assertion. Notice-and-comment rulemaking would, of course, ensure that FDA receives factual information from a variety of stakeholders on the validity of this fundamental premise.⁵¹

FDA has also failed to explain why the approach put forth in the IVDMIA Draft Guidance effectuates the objectives of the FDCA as well as, or better than, the Agency’s original approach. And, despite the existence of the much more detailed CLIA framework

⁴⁹ Yale-New Haven Hosp. v. Leavitt, 470 F.3d 71, 80 (2d Cir. 2006) (citations omitted) (invalidating a 1986 HCFA Manual Provision which “altered historical practice”).

⁵⁰ IVDMIA Draft Guidance at 2.

⁵¹ HPM notes that at the February 8, 2007 meeting to discuss IVDMIAAs, many speakers – including some that were supportive of FDA’s objectives – were concerned by the lack of clarity in the IVDMIA Draft Guidance. APA rulemaking provides the best vehicle for addressing and resolving these types of issues. Permitting comments to the IVDMIA Draft Guidance does not resolve these types of issues. For example, unlike APA rulemaking, FDA is not obliged to address the significant comments in finalizing a guidance document.

for regulation of clinical laboratories, the Agency has offered no justification for, or detailed explanation of its statutory authority to take, the approach described in the IVDMIA Draft Guidance other than its view that LDTs meet the FDCA definition of “device.”

Finally, FDA has not described alternative methods to address its concerns, such as working with CMS to improve the expertise and ability of clinical laboratories through enhanced CLIA regulatory controls. Thus, regardless of whether FDA’s reversal constitutes a substantive rule subject to APA notice-and-comment rulemaking, the absence of a detailed explanation renders such reversal arbitrary and capricious on a substantive level.

IV. Conclusion

As discussed above, FDA’s publication of the IVDMIA Draft Guidance, and its attempt to regulate clinical laboratories generally, exceeds the Agency’s authority under the FDCA and conflicts with Congress’ intent through CLIA to confer exclusive regulatory authority over clinical laboratories to other federal agencies. Moreover, the means by which FDA is attempting to assert its authority over clinical laboratories and their LDT services, profoundly altering its historical 30-year practice, should proceed through notice-and-comment rulemaking, and does not adequately explain or justify the change. Accordingly, HPM concurs with the requests of WLF that FDA “immediately cease and desist seeking to regulate [LDTs] as medical devices” and that if FDA continues to believe it has authority to regulate LDTs as medical devices, the Agency “proceed with proper notice-and-comment rulemaking, as required under the APA.”

Respectfully submitted,

A handwritten signature in blue ink, appearing to read "Jeffrey N. Gibbs".

Jeffrey N. Gibbs
Hyman, Phelps & McNamara, P.C.

JNG/JBD/rd

cc: 2006D-0347