

MEMORANDUM

Date: August 16, 2006

Re: Regulation of laboratory developed tests (“home brew” assays) as medical devices

ISSUES

There are reliable reports that FDA (OIVD) is contacting individual clinical laboratories that have developed and are offering to clinicians laboratory developed tests (LDTs), as defined clearly in recent years, and asking them to meet with the Agency to describe their assay(s) and operations. Further, laboratory owners are reporting that some of the Agency’s senior management have determined that certain of these assays, historically and explicitly exempted by FDA from regulation as medical devices, are now “regulatable” as medical devices. FDA is informing some laboratory owners that their home laboratory developed tests are, therefore, “unapproved medical devices” and, by extension, their laboratories are “manufacturers” of in vitro diagnostic products regulated by FDA under the Federal Food, Drug & Cosmetic Act (FFDCA).

I. These assays fit squarely under FDA’s long-standing policy exempting laboratory developed tests from regulation by FDA.

These assays fit squarely into FDA’s widely understood and longstanding definition of “home brew,” *i.e.*, laboratory developed or “in-house test methods” regulated by CLIA (and by some State agencies), but not previously subjected to FDA premarket review and clearance. The operations of some, possibly all, of these companies do not include any of those premarket or post-market activities that previously have triggered FDA Warning Letters to clinical laboratories. For example, there is no sharing of any aspect of the company’s assay for third party use (as with the Correlomics Systems, Inc. Warning Letter). See Letter from Steven I. Gutman, M.D., M.B.A., Director, OIVD to Peter J. Levine, President & CEO, Correlomics Systems, Inc. (July 12, 2004). Nor has there been any “introduction . . . into commercial distribution” of unapproved “Test Package(s)” as with the Access Genetics Warning Letter. See Letter from Steven I. Gutman, M.D., M.B.A., Director, OIVD, to Ronald McGlennen, M.D., President, Access Genetics (August 1, 2005).

It is confirmed that some, possibly all, of these companies are exactly what they appear to be: CLIA certified “high complexity” laboratories. To quote CLIA: “...the term ‘laboratory’ or ‘clinical laboratory’ means 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, of the assessment of the health of, human beings.” 42 U.S.C. 263(a) (emphasis added)

Again, some, possibly all, of these assays also are exactly what they appear to be: laboratory developed (or “home brew”) tests. To quote a 2003 Guidance from the FDA: the assays incorporate “general purpose reagents [and] general purpose instruments [used] by a laboratory to set up an in-house (“home brew”) test or laboratory testing service. While specimens can [and do] travel to the laboratory setting up this service, the test itself is not marketed outside of the single laboratory setting up this service. * * * **It is the responsibility of the laboratory to develop a recipe for the [home brew] test at hand and to take responsibility for establishing and maintaining performance. . . . * * *** Although not part of the [ASR/home brew] rule, **FDA has indicated that FDA is not requiring the in-house test**

to go through premarket FDA review.” See FDA, CDRH, *Analyte Specific Reagents; Small Entity Compliance Guide; Guidance for Industry*, at 2-3 (Feb. 26, 2003) (emphasis added).

These laboratory services also meet the laboratory medicine community’s definition of a LDT. (In professional laboratory and medical circles, the nomenclature “laboratory developed test” is used, but it defined interchangeably with “home brew.”) The medical leadership sometimes has to explain why there is a need for these laboratory developed tests: to meet otherwise “*unmet clinical and medical needs.*” Sometimes tests need to be developed quite rapidly in response to new infectious (mutating HIV genotypes) or vector-borne diseases, as with the West Nile virus. Employing such laboratory developed tests often is the *only* way that physicians and public health epidemiologists reliably can determine which specific pathogen is causing a patient’s symptoms and be able to select highly specific treatment regimens.

Two additional attributes of laboratory developed tests generally are identified as accepted adjuncts to CLIA regulation for assuring patient safety: the medical peer reviewed literature documents clinical utility and standard of care guidelines recommend how and when to use the test. H. Faruki, DrPH, et al. Laboratory Developed Tests--Current Practices to Assure Validity. ACLA presentation (Oct. 17, 2002).

All of these definitions and attributes of laboratory developed tests describe the assays facing FDA challenges now. Some, possibly all, of the companies did the premarket work needed to develop all aspects of the assays in-house, with these peer-driven validation standards, as well as CLIA required validation and documentation, as their regulatory benchmarks. And they completed this analytical and clinical validation before the first patient test result was reported, as required by CLIA. See 42 U.S.C. 493.1253(b).

FDA repeatedly has assured the medical and laboratory communities that it will not regulate LDTs as medical devices. These assays are LDTs. They comprise nothing beyond what FDA has exempted historically from regulation under its established policy.

II. Extending FDA medical device regulation to laboratory developed tests is inconsistent with the regulatory framework established by Congress in CLIA.

FDA's reading of the medical device amendments under the FFDCAs as extending jurisdiction to all laboratory developed test systems essentially nullifies CLIA as the regulatory oversight framework for laboratory test systems. CLIA regulations recognize that clinical laboratories can run three types of test systems¹ with reference to FDA-clearance or approval: (1) test systems cleared or approved by FDA and run by the laboratory without modification; (2) test systems cleared or approved by FDA and run by the laboratory after modification by the laboratory; and (3) test systems not subject to FDA clearance or approval. CLIA requirements to establish or verify test system performance characteristics vary depending upon whether the test system has FDA clearance or approval and/or is modified by the laboratory:

¹ The CLIA regulations define test systems 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. Section 493.2. FDA staff have indicated in at least one company’s case that the “whole test system” would be subject to regulation by FDA under the FFDCAs—the same whole “test system” that is subject to regulation by CMS under CLIA.

- Laboratories that introduce test systems not subject to FDA clearance or approval or that modify FDA-cleared or approved test systems establish for each test system the following performance characteristics: (i) accuracy; (ii) precision; (iii) analytical sensitivity; (iv) analytical specificity; (v) reportable range of test results for the test system; (vi) reference intervals (normal values); and (vii) any other performance characteristic required for test performance. 42 C.F.R. § 493.1253(b)(2).
- Laboratories that perform unmodified, FDA-cleared or approved test systems are required to demonstrate only that they can obtain accuracy, precision, and reportable ranges comparable to those established by the manufacturer and to verify that manufacturer's reference intervals (normal values) are appropriate for the laboratory's patient population. *Id.* § 493.1253(b)(1).

If FDA's jurisdiction under the FFDCa is read to extend to all laboratory developed tests, then the framework carefully set out in the CLIA regulations would make no sense. There would be no such thing as a test not subject to FDA clearance or approval—all tests would be subject to FDA clearance or approval. A laboratory would not be permitted to modify an FDA-cleared or approved test system without subjecting the laboratory to FDA clearance or approval requirements. Laboratories would never be in a position to *establish* performance characteristics for methods developed wholly “in-house” as comprehended by the CLIA regulations. Every laboratory would be required to obtain FDA clearance or approval for all test systems, with one exception only, *i.e.*, for those test systems where FDA clearance or approval is obtained by an IVD manufacturer, the test system is purchased by a clinical laboratory, and the laboratory uses that test system exactly as indicated in the FDA-cleared labeling.

It is unreasonable to conclude that the Department of Health and Human Services would issue regulations specifying requirements for compliance under CLIA that describe test systems *not* subject to FDA clearance or approval if all test systems are subject to FDA clearance or approval under the FFDCa.

Further, it is untenable for FDA to suggest that Congress intends that the FFDCa essentially shall override CLIA. Congress has directed the Centers for Medicare and Medicaid Services (CMS) to enforce CLIA requirements to assure patient access to innovative testing and to “provide an appropriate level of consumer protection.” See 61 Fed. Reg. 10, 484 (March 14, 1996); 62 Fed. Reg. 62, 243 (Nov. 21, 1997). Therefore, it is very unlikely that a court would find that FDA has jurisdiction to regulate as a new medical device a clinical laboratory's novel “in-house test method” that is regulated by CLIA. See 42 U.S.C. 263(a).

Congress has spoken clearly on the regulation of clinical laboratory services: the painfully detailed regulation of laboratory methods *by methodology* enacted by Congress in CLIA in 1988 (and the compromises struck over four years of rulemaking thereafter) take precedence over the broadly drawn provisions of the Medical Device Amendments enacted twelve years earlier (1976). When Congress has reached a “compromise between groups with marked but divergent interests,” as in CLIA, “courts and agencies must respect and give effect to those . . . compromises.” Ragsdale v. Wolverine World Wide, Inc., 535 U.S. 81, 94 (March 19, 2002).

One of the central features of CLIA is the balance Congress struck between maintaining patients access to state-of-the-art “in-house laboratory test methods,” while assuring the validity and quality of such testing. FDA's current foray into regulating some of these CLIA-regulated laboratory tests threatens to “subvert the careful balance” struck by CLIA and cannot be allowed to continue. With no public discussion around creating and enforcing this year's new boundaries, the random targeting of laboratories or algorithms used in medical practices and inconsistent enforcement among similarly situated entities would be unavoidable. FDA cannot impose this sweeping policy shift without first soliciting and evaluating comments from those affected directly and all other interested parties.

FDA's assertion of jurisdiction over conduct that Congress has said is regulated by CMS is impermissible. The courts are clear and consistent, even when acknowledging that substantial deference should be paid to FDA's interpretation of its public health missions: "FDA cannot simply take what Congress has not granted." See FDA v. Brown & Williamson Tobacco Corp., 529 U.S. 120 (2000).

III. Extending FFDCa regulation to laboratory developed assays, without providing a clear articulation of the criteria used to determine those assays that will and those assays that will not be regulated, and without providing notice and opportunity for the regulated community and other interested persons to comment on the appropriate regulatory pathway for these assays, would violate the requirements of the APA. It also would violate FDA's own rules on communicating "new or different regulatory expectations . . . for the first time" under 21 C.F.R. Section 10.115(e). (Emphasis added)

FDA apparently infers that its jurisdiction to regulate all laboratory developed assays as medical devices comes from the broad wording of the definition of a medical device under the FFDCa.² Although this definition is broad, it does not extend FDA jurisdiction to services that are performed with these devices. This is clear from the history of FDA's extension of jurisdiction in the context of laboratory developed tests, from regulations exempting from FDA jurisdiction entities that provide services involving the use of devices, and from the framework for regulation of clinical laboratory services negotiated by the medical community under CLIA and its implementing regulations.

Where FDA has extended jurisdiction in the context of laboratory developed tests, it has limited its reach to those that manufacture and distribute the ingredients used to perform laboratory tests, such as analyte specific reagents (ASRs). FDA's regulatory reach has extended only to tangible "things"—not to services.³ FDA has never sought to regulate entities performing laboratory services simply because those entities use FDA-regulated (or "regulatable") ingredients. In fact, FDA regulations exempt from regulation: "[p]ersons . . . whose major responsibility is to render a service to provide the consumer i.e., patient, physician, laymen, etc.) with a device or the benefits to be derived from the use of a device; for example, . . . [a] clinical laboratory."⁴ 21 C.F.R. section 807.65(i).

Additionally, it is clear that FDA is *first* communicating a shift in policy on regulation of LDTs with private communications directed to individual persons or firms, contravening its own GGP rules. Under 21 C.F.R. section 10.115(e), "[Good Guidance Practices] must be followed whenever regulatory expectations that are not readily apparent from the statute or regulations are *first* communicated to a broad public audience." (Emphasis added)

The purpose of these GGP regulations is to prevent precisely what OIVD is doing now, *i.e.*, the *first* signal that there is a new agency policy is being communicated impermissibly (in private meetings with individual firms or through private letters that are directed to individual entities). In the 1997 Federal Register notice announcing the creation of GGPs, FDA stated that the agency "may not use documents

² "[A]ny instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part of accessory, which is intended for use in the diagnosis of disease or other conditions is a device." FFDCa § 201(h), 21 U.S.C. § 321(h).

³ Some at FDA take the position that the "thing" that is a medical device is the novel algorithm or equation used to calculate a test result. However, there is nothing tangible about any equation—it is simply a mathematical concept. Further, in any "plain meaning" analysis, the true scope of FDA's proposed new jurisdiction becomes evident: "algorithm" is defined as "[a]step-by-step protocol, as for management of health care problems." And "protocol" is defined as "[t]he format and procedure that govern the transmitting and receiving of data." www.TheFreeDictionary.com (medical version)

⁴21 C.F.R. § 807.65(i).

and other means of communication that are excluded from the definition of guidance document to informally communicate new or different expectations for the first time.” 65 Fed. Reg. 56,468, 56,474 (Sept. 19, 2000). FDA is failing to comply with its GGP rule.

If FDA moves forward without the bright line criteria required for both regulators and regulated entities, many practical problems will arise. FDA has not established any inclusionary boundaries for determining whether to regulate laboratory developed assays. Many boundaries mentioned in FDA meetings are simply unworkable:

- Genetic testing methods developed by laboratories cannot be the inclusionary boundary because that would include a large number of the tests that FDA has clearly stated it will not regulate due to the “home brew” exemption (regardless of whether there are or are not ASRs employed in a laboratory’s in-house test system).
- A clinical laboratory’s use of a novel predictive algorithm cannot be the inclusionary boundary because algorithms are used routinely by laboratories and clinicians, and new ones are being introduced regularly.
- Mathematical transformation from raw data to reported test results cannot be the inclusionary boundary. This would bring in all genetic tests (100%) and many standard laboratory tests.
- The FDA jurisdictional trigger cannot be the creation and use by a single laboratory of novel software because FDA has communicated that calculating a test result by hand, even by a company-employed physician’s hand, would still result in FDA asserting jurisdiction and not be exempt as “the practice of medicine.” (FDA officials have provided no legal rationale for why hand-scored test results could be devices.)
- The characteristics of the entity offering a novel laboratory developed test or service cannot be the inclusionary boundary, *e.g.*, a for-profit company and an academic medical center are in all relevant aspects indistinguishable in their capabilities and operations.

Finally, CDRH must consider the relationship of its response to these issues in the context of its ASR rule. Specifically, would a laboratory providing a service identical to one or more of those under scrutiny now, utilizing an equation or algorithm to produce a reportable test result, be subject to regulation if it bought one or more ASRs for use in its assay? The preamble to the ASR regulation indicates that the answer would be, “No.” A laboratory owner’s ability to find and purchase ASRs for use in its home brew, which is not an option for some of these companies because early projections of low volume make them unattractive to ASR manufacturers, cannot be the basis for distinguishing those otherwise identical assays that will be regulated as medical devices from those that will be exempt from such regulation.

Without clearly articulating the factors that can cause any laboratory developed test to be regulated as a device, FDA violates the APA. The companies under scrutiny have asked for guidance on these factors and have been given inconsistent and widely diverging answers. Until guidance is developed in an appropriate and legally compliant manner, regulating these clinical laboratory services as medical devices is impermissible.

IV. Extending regulation to genomic assays or to diagnostic services involving computations or algorithms means that FDA would be extending premarket review and other requirements under the FFDCA to a very broad range of services that have for many years fit under the “home brew” exemption and/or the practice of medicine exemption from FDA regulation.

If FDA were to regulate genomic assays or other laboratory services that employ computations or algorithms to produce test results as a medical device, this decision would have far-reaching consequences that extend beyond the individual laboratory and would be inconsistent with FDA’s regulation of other treatment tools. There are a large number of products currently marketed that involve algorithms or that perform other calculations that are then used in a clinical or diagnostic context. There are multiple versions of software available to physicians that provide a likely set of diagnoses based on a list of symptoms, test results, and other clinical data. Software that identifies medication issues and errors also is available to pharmacists.⁵ And there are hundreds of nomograms, decision aids “designed to help physicians and patients decide which treatment approaches will result in the greatest benefit.” (See, *e.g.*, the Memorial Sloan Kettering “Prediction Tool: Prostate” (Attached).

These services assist health care professionals in making diagnoses and treatment decisions that affect patient health, but FDA has not regulated them. FDA’s historical approach and policy has been that these new algorithms or decision aids can be used in diagnostic and treatment decisions, indeed are essential to keeping patient care current with the state-of-the-art, and are not subject to FDA premarket controls. The sheer pace with which such decision aids appear makes their FDA regulation as new medical devices impossible. For example, a recent article in the New England Journal of Medicine describes a model by which to identify germ-line DNA mismatch-repair genes important to the diagnosis of colorectal cancer and the management of the disease. Rebecca A Barnetson, Ph.D. et al., Identification and Survival of Carriers of Mutations in DNA Mismatch-Repair Genes in Colon Cancer. 354 *New Engl. J. Med.* 2751 (June 29, 2006). This is the context in which FDA must consider the CLIA-regulated information that genomic assay providers and other laboratories deliver routinely to practicing physicians to help them fully understand individual test results. See 42 C.F.R. Sec. 493.1291 “Standard: test report”.

FDA has not regulated equations or algorithms used to make decisions about patient health as medical devices. Even assuming these algorithms are devices—a point the providers of the algorithms would dispute—singling out any one company’s service as a medical device is arbitrary, capricious, and inconsistent with agency practices. FDA violates the APA by subjecting any one assay to device regulation without providing clear criteria and by changing the FDA’s prior policy without providing an opportunity for public comment. Any FDA decision that a company’s assay is a device because of the use of a novel equation or algorithm to calculate a test result that can be applied diagnostically also has consequences far beyond laboratories and would constitute unlawful interference with the practice of medicine. Fundamentally, FDA regulation of laboratory developed tests would disregard the carefully negotiated Congressional limits on interference with physicians practicing laboratory medicine (and physicians in other specialties using these specialists test results) addressed throughout the CLIA legislative history and addressed in four years (1988-1992) of subsequent CLIA rulemaking.

The implicit scope of what CDRH is doing is untenable, as well as unlawful. The medical community has had clear understandings with Agency leaders for decades that boundaries carefully negotiated around regulating “the practice of medicine” would be respected. Today’s foray with these companies may only

⁵ Such software programs include: Massachusetts General Hospital Laboratory of Computer Science’s DXplain®; Isabel Healthcare’s Isabel Diagnosis Reminder System and Isabel Knowledge Mobilizing System; Pharmacy Healthcare Solutions’ Medstorm™; and Medical Information Technology, Inc.’s MEDITECH.

involve physicians licensed as pathologists and primarily affect physicians who provide essential care to cancer patients, but tomorrow's forays could take the Agency into any area of medicine it may choose where there is some type of algorithm+software decision aid in use.

The College of American Pathologist's (CAP) position on the regulation of these in-house assays, including "genetic" testing, is clear: "***CAP views genetic testing as a medical service*** and, in this context, CAP strongly recommends that the practice of genetic testing be governed through consensus among practitioners via professional organizations. . . . * * * ***Genetic tests are not fundamentally different from other highly complex clinical laboratory tests. Adequate standards for [their] conduct . . . are included under the current CLIA regulations.***" (Emphasis added)

These CAP comments on regulation of "genetic" tests (offered to the Secretary's first Advisory Committee and responding to its *Final Recommendations for Oversight of Genetic Testing*) are significant. One of the Advisory Committee recommendations, excerpted here, was that "**The Food and Drug Administration (FDA) should be the lead federal agency responsible for reviewing, approving and labeling of all new genetic tests.**" 65 Fed. Reg. 21, 093, 21, 095 (April 19, 2000). CAP's response is captured in the paragraph above and the statements below:

"CAP questions why [the Advisory Committee] has recommended FDA review of all new genetic tests. * * * . . . it is apparent that [the Committee] did not receive a clear directive from the public that additional oversight must include FDA oversight. ***CAP is opposed to FDA oversight for [four] reasons: * * * . . . (2) CAP questions the ability of the FDA to develop flexible mechanisms for review of genetic tests. FDA's statutory authority neither provides for flexibility or for contracting [review to third parties] with flexibility in mind. (3) The FDA has historically chosen to not review the home brew tests and CAP questions if the resources are [now] available. Current FDA approval processes take years to complete. Given the fact that genetic tests are being developed every day, CAP wonders whether a system to review genetic tests by the FDA could be implemented in a timely fashion. (4) . . . since the CLIA already mandates standards developed according to complexity, CAP questions whether additional levels of scrutiny are needed.***"

Letter from Paul Bachner, M.D., CAP to Edward R.B. McCabe, M.D., Ph.D., Chair, Secretary's Advisory Committee on Genetic Testing, (May 24, 2000).

FDA's authority to regulate medical devices under the FFDCA must be considered in the specific context of prior actions and competing authorities such as CLIA. Without such contextual thinking, overreaching occurs. See FDA v. Brown & Williamson Tobacco Corp., 529 U.S. 120 (2000).

V. Compliance with both the FFDCA and CLIA essentially is unattainable in a clinical laboratory operation.

FDA's regulations require manufacturers of finished medical devices to comply with Quality System Regulations (QSRs). See 21 C.F.R. Part 820. If laboratory testing services were to be considered medical devices, clinical laboratories would be required to follow QSRs as manufacturers of finished medical devices. The requirements placed on manufacturers under QSRs include quality audits, design controls, production and process controls, validation, labeling procedures, and maintaining records. See *id.* To be compliant with CLIA, laboratories must follow quality control, validation, records, and auditing procedures under CLIA regulations, which are designed to ensure quality standards for all laboratory

testing. See 42 C.F.R. Part 493. Though the requirements under QSRs and CLIA share similar goals, the exact procedures by which quality control is accomplished under each separate regulatory scheme are different and sometimes in opposition to each other.

For example, the design control requirements under QSRs demand that manufacturers establish and maintain detailed design development and review procedures, as well as detailed “procedures for the identification, documentation, validation or where appropriate verification, review, and approval of design changes before their implementation.” 21 C.F.R. § 820.30(i); see also *id.* § 820.30(c). Quite simply, this is not how laboratories operate. These companies did not develop their assays in accordance with design controls; no laboratory complies with section 820.30. To comply with design controls, laboratories would need to completely revamp the way that they develop tests. A home brew laboratory test may consist of multiple markers. If the laboratory changes one of these markers or the way that it processes samples, the entire test would be required under QSRs to undergo design review to satisfy the formal procedures laid out by FDA. Moreover, compliance with FDA’s design controls would significantly hinder laboratories’ ability to make necessary changes and modifications to tests and test systems as diseases themselves change, or to make improvements to laboratory tests.

Similar unworkable burdens would be placed on laboratories under the QSR production and process control requirements, which require standard operating procedures (“SOPs”) that define and control the manner of production. *Id.* § 820.70(a)(1). CLIA does not require these SOPs; therefore, laboratories do not currently have the type of SOPs expected by FDA in place. Even the simplest of finished medical devices require extensive SOPs, and developing, implementing, following, and maintaining SOPs is extremely demanding. To require laboratories to conform to this FDA requirement would be to establish a system where every laboratory was non-compliant.

Additionally, if clinical laboratories were regulated by FDA, they would be required to submit to FDA Medical Device Reports (MDRs) under 21 C.F.R. Part 803. These reporting requirements are quite detailed. Currently, laboratories are not obligated to submit MDRs to FDA. Laboratories do not have in place the systems or procedures necessary to follow FDA’s MDR regulations. Requiring laboratories to submit MDRs would require the development of an entirely new infrastructure for each laboratory.

FDA regulations also govern the promotion and labeling of medical device products. Laboratories currently promote laboratory tests and services. If FDA regulated clinical laboratory services and laboratories themselves, presumably FDA would have jurisdiction over the promotion of home brew tests and laboratory services. This would represent FDA regulation in an area that the agency has never before regulated. It would raise questions over the scope of FDA regulation, e.g., promoting a service versus promoting a device. It also would raise First Amendment issues. See *Thompson v. W. States Med. Ctr.*, 534 U.S. 1077 (2002).

Additional questions would arise over the content of laboratory reports. If laboratories were FDA-regulated entities, would a laboratory report be considered to be promotion of a laboratory test or service? Would a laboratory report be considered to be labeling for the test or service? If so, would laboratories then be required to conform laboratory reports to the requirements for labels and to submit changes to laboratory reports to FDA as changes to labels? See, e.g., 21 C.F.R. Sec. 807.81(a)(3).

These difficulties are compounded by the absence of a definition of what is the device itself. Some in FDA have said that “the whole system” that comprises a home brew assay is the device. That would suggest that every step that a laboratory takes would now be subject to QSRs and to all other device (and device manufacturer) regulations. Others in FDA have said that only the calculations that produce test results with some home brew assays are the device “component” subject to FDA regulation. This broad,

ill-defined, and periodically conflicting scope of what is the device and how it would be regulated further underscores the impermissibility of FDA acting now to regulate these assays.

CONCLUSION

It is clear that the Agency does not fully appreciate the consequences of imposing device regulations on laboratories and medical practices, especially the incompatibility of QSR and CLIA quality oversight requirements. Compliance with one set of regulations virtually guarantees non-compliance with the other. FDA must step away from imposing its regulations on assays that fit squarely into FDA's historical definition of these exempt "home brew" tests until it has carefully and publicly adopted a regulatory approach that complies with applicable law.

To date, FDA has not regulated clinical laboratories as manufacturers of medical devices. As Dr. Gutman has publicly acknowledged, "manufacturers and labs are different entities." Genetic Tests: SACGT Asks FDA to Fill in Details of Premarket Process, *The Gray Sheet*, Vol. 27, No. 36, at 8 (Sept. 3, 2001). The same reasons that kept FDA from extending its jurisdiction to regulating laboratory developed tests in the past pertain today, even more so given the presence of pandemic pathogens and the growing number of Baby Boomers facing cancers and other debilitating diseases that will use all of the "high complexity" laboratory infrastructure this country can provide. Moreover, applied to clinical laboratories, FDA's regulatory regime will create a situation that is unworkable both for laboratories and for FDA. FDA's actions going forward must be anchored in policies that reflect these limits on what CDRH can and should be doing. They also must be lawful under the APA and comply with other legal requirements.⁶

Attachments: Timeline on "Home Brew" Policy Developments

Memorial Sloan-Kettering – "Prediction Tools: Prostate" (Kattan nomogram)

⁶ "Agency interpretations that take place in the many less formal contexts . . . (e.g., opinion letters, policy statements, agency manuals, and enforcement guidelines, 'all of which lack the force of law') can still be 'entitled to respect', . . . but only to the extent that [they] have the power to persuade." G. Costello. "Statutory Interpretation: General Principles and Recent Trends," Congressional Research Service, at CRS-25 (March 30, 2006). The "weight of [an Agency's] judgment in a particular case will depend upon *the thoroughness evident in its consideration, the validity of its reasoning, its consistency with earlier and later pronouncements*, and all those factors which give it power to persuade, if lacking power to control." Skidmore v. Swift & Co., 323 U.S.134, 140 (1944) (emphasis added).