

## 6. Laboratory Developed Tests

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### I. Introduction

Laboratory tests can come to market through several different pathways. In the vast majority of cases, tests are manufactured by medical device companies that market a complete test “kit,” which typically includes the necessary reagents, instructions, statements regarding the intended use and other information about the test. As these tests are sold to laboratories, hospitals or physicians’ offices in interstate commerce, they must typically be cleared or approved by the Food and Drug Administration (FDA) through either the premarket notification<sup>1</sup> or premarket approval (PMA) processes.

However, some laboratories also develop their own tests in-house, for use by the laboratory entity itself. In that case, the laboratory may purchase reagents from outside suppliers (or create them itself), and then develop its own proprietary test to use within the laboratory. The laboratory never sells the *test kit* to other laboratories, hospitals or doctors; rather, it only offers the testing *service* to them and performs this test, when ordered, in-house. These tests, referred to as laboratory developed tests (LDTs), do not typically go through the FDA approval or clearance process.<sup>2</sup>

LDTs present some unique regulatory questions. For example, does FDA have the authority to regulate these tests if there is no kit introduced in interstate commerce? If so, how would such regulation overlap with the Clinical Laboratory Improvement Amendments (CLIA),<sup>3</sup> which regulate virtually all laboratories performing testing? Regardless of whether FDA regulation is proper, what assurances exist that LDTs are safe and effective? These questions have been the subject of frequent discussion since the first development of LDTs, and even more so recently.

This chapter begins by providing a general overview of the regulation of LDTs, including FDA and CLIA regulation. It then addresses FDA’s scrutiny of LDTs and the recent position that FDA has taken regarding a subset of LDTs known as In Vitro Diagnostic Multivariate Index Assays (IVDMIAs). It then closes with a discussion of other issues and concerns that have been raised by FDA regarding LDTs, including potentially new policy positions stated by an FDA official at a recent conference.

## II. Overview of LDT Regulation

FDA takes the position that LDTs are medical devices over which it has authority, but that it has chosen to exercise enforcement discretion over them. In FDA's Final Rule on Analyte Specific Reagents (ASRs), issued in 1997, FDA discussed what it referred to as "in-house" tests. It declined to require that all such tests be treated as Class II or Class III medical devices; however, FDA did note that "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."<sup>4</sup> FDA declined to regulate such tests at that time, however, because it noted that the use of such in-house tests had contributed to "enhanced standards of medical care in many circumstances and that significant regulatory changes in this area could have negative effects on public health."<sup>5</sup>

Similarly, in a recent draft guidance document on IVDMIAs, which is discussed in greater detail below, FDA reiterated this position and noted "the agency has generally exercised enforcement discretion over standard LDTs, *e.g.*, LDTs that use primarily analyte specific reagents, general purpose reagents ... , general purpose laboratory equipment ... other laboratory instrumentation ... and controls."<sup>6</sup> As discussed in greater detail below, the laboratory industry has not agreed with FDA's position that it has jurisdiction over LDTs.

Even though LDTs are not usually subject to FDA enforcement, they are still subject to federal oversight. Virtually every laboratory performing testing in the United States must meet CLIA requirements, which are primarily enforced by the Centers for Medicare & Medicaid Services (CMS), rather than by FDA. CLIA establishes a comprehensive regulatory scheme for laboratories, including quality control requirements, personnel qualifications and proficiency testing (PT) mandates.<sup>7</sup> Proficiency testing is the system by which laboratories test particular samples and then are graded on their results by an outside agency, such as the College of American Pathologists (CAP).<sup>8</sup> Laboratories regulated under CLIA must comply with more rigorous requirements as the complexity of the testing increases. For example, laboratories performing testing classified as waived must meet minimal regulation, and must usually only follow the manufacturer's instructions for the test.<sup>9</sup> However, laboratories performing testing classified as high complexity testing must meet strict personnel requirements, both in the types of personnel required and their qualifications.<sup>10</sup> Laboratories performing "moderately complex" testing meet requirements between the two.<sup>11</sup> FDA is responsible for determining the complexity of tests when it approves or clears new in vitro diagnostic products.<sup>12</sup> Tests, such as LDTs, that do not go through the categorization process as part of FDA approval or the clearance process are considered high complexity.<sup>13</sup>

CLIA imposes special requirements on tests that are not subject to FDA clearance or approval, such as LDTs. One section of CLIA specifically discusses the quality assurance obligations of laboratories that are using testing not subject to FDA clearance or approval. If a laboratory “introduces a test system not subject to FDA approval or clearance,” the regulations require it to establish “performance specifications” for the tests before reporting test results. These include accuracy, precision, analytical sensitivity, specificity, reportable ranges and others required for test performance.<sup>14</sup> CMS has issued guidance for CLIA inspectors, which states that this specific provision is intended to apply to tests developed with ASRs, which would include most LDTs.<sup>15</sup> Another section of the CLIA requirements states that if there is no PT program that covers the specific testing offered by the laboratory, which might be the case for many LDTs, then the laboratory must establish its own procedures to verify the accuracy of its testing.<sup>16</sup>

Over time, there has been disagreement over the extent of FDA’s jurisdiction over LDTs and the impact of CLIA on FDA’s authority in this area. Representatives of the laboratory industry, for example, have generally taken the position that FDA does not have jurisdiction over LDTs. First, they reason that Congress intended CLIA, rather than the Federal Food, Drug, and Cosmetic Act (FDCA), to apply to laboratories, given CLIA’s pervasive regulatory scheme; therefore, they conclude, LDTs performed by laboratories should be subject to CLIA, rather than the FDCA.<sup>17</sup> These stakeholders also point out that FDA only has jurisdiction over “medical devices” that are introduced into interstate commerce; however, with LDTs, no device is moving in commerce for FDA to regulate. Laboratories, according to this view, furnish a testing *service* to physicians and patients, which does not constitute a “medical device.” If there is no device, then there is nothing over which FDA can exercise its jurisdiction.<sup>18</sup>

The American Clinical Laboratory Association (ACLA), which represents clinical laboratories, explained this position in comments to FDA. It stated:

The components of LDT processes are not marketed as kits or test systems, and they are not physically distributed or delivered outside the laboratory. Instead, laboratories provide written reports of the results to ordering physicians after the laboratories have performed the tests within their laboratories. Thus, clinical laboratories that develop and perform LDTs are selling *services* to outside entities; they are not selling any identifiable *medical device*...laboratories performing these tests are engaged in a process that does not involve any sale or distribution of a medical device to a third party.<sup>19</sup>

Other organizations have supported this position. For example, in 2008 the Washington Legal Foundation (WLF), a public interest law and policy center, filed a Citizen Petition with FDA.<sup>20</sup> The Citizen Petition argued that FDA did not have the authority to regulate LDTs. According to the WLF, Congress intended for laboratories, and LDTs, to be regulated under CLIA, because it regulates virtually every laboratory in the country performing testing, including those doing LDTs.<sup>21</sup> The WLF argued that Congress intended for laboratories and LDTs to be regulated under CLIA, rather than under the FDCA. Because many new tests are first developed as LDTs, WLF also noted that FDA's action could have adverse consequences for patients and health care generally.<sup>22</sup> The WLF Citizen Petition was similar to an earlier Citizen Petition from the same organization submitted in October 1992 and subsequently denied by the agency.

Not surprisingly, other stakeholders have taken a different view. In December 2008, Genentech, a biotech company, filed its own Citizen Petition, which took a different position.<sup>23</sup> Genentech argued that FDA had jurisdiction over LDTs and should exercise control over all in vitro diagnostic products, regardless of whether they were LDTs or more traditional kits.<sup>24</sup> Genentech pointed out that the numbers and types of LDTs were increasing and that it was important to ensure that all tests were accurate, reliable and valid.<sup>25</sup> Genentech also expressed concern that some LDTs were intended to be used with drugs and biologics, including those that the company itself manufactured.<sup>26</sup> According to Genentech, such tests were being marketed to, and used to, guide patient treatment decisions, without FDA review of the claims being made. Laboratory organizations filed comments in opposition to Genentech's petition, although other device manufacturers were supportive.<sup>27</sup> At this point in time, FDA has not acted on either the WLF or the Genentech Citizen Petition, although FDA officials have stated both are under review.

Most recently, CAP, which accredits many clinical laboratories under CLIA, issued a statement proposing a new approach to the regulation of LDTs. It proposed that laboratory accrediting and inspection organizations should review the clinical support for most low-risk LDTs as part of their usual oversight process. FDA would only be required to review LDTs that were at the very highest risk level, although how risk levels were to be determined was left unclear.<sup>28</sup>

### **III. FDA Scrutiny of LDTs**

As discussed above, FDA has stated that it has authority over LDTs, but has usually chosen to exercise its enforcement discretion. However, FDA has chosen to act on some occasions, where it believed that entities were offering tests they claimed were LDTs, when they did not

in fact meet the definition. For the most part, FDA has acted by sending letters to the company or companies involved and requesting background on the tests at issue. In most instances, those receiving such letters have chosen to withdraw the test or go through FDA procedures, rather than contest FDA's jurisdiction.

In 2004, for example, FDA wrote to Correlogic Systems, which had developed a test called OvaCheck, for the early identification of ovarian cancer. FDA wrote to Correlogic, stating that it was concerned because Correlogic had licensed its software to clinical laboratories that used it when offering Correlogic's test. Although Correlogic argued that its testing should not be subject to FDA regulation because oversight under CLIA was sufficient, FDA rejected this approach. It concluded that Correlogic was required to obtain FDA approval or clearance before licensing the test software to other laboratories.<sup>29</sup> As a result, Correlogic withdrew the software from its laboratory partners, and instead analyzed the information on site, within its own facility.<sup>30</sup>

Several years later, FDA wrote to the Laboratory Corporation of America (LabCorp) about a different ovarian cancer test, OvaSure, which LabCorp stated qualified as an LDT. FDA took the position that the test had been developed at Yale University, and had simply been licensed to LabCorp. As a result, according to FDA, the test did not qualify as an LDT and was required to go through FDA approval or clearance.<sup>31</sup>

FDA has exercised some control over LDTs in another way as well. Many LDTs are created using analyte specific reagents (ASRs), which are subject to specific FDA requirements, including limits on the claims that can be made about them, to whom they can be sold and how they can be labeled. As part of the ASR rule, FDA required that laboratories offering tests using ASRs include a specific disclosure that would demonstrate the test created was not approved by FDA. That disclosure states:

This test was developed and its performance characteristics determined by [laboratory name]. It has not been cleared or approved by the U.S. Food and Drug Administration. Further, many laboratories use a similar statement on most LDTs.<sup>32</sup>

Thus, although the ASR rule primarily regulated the sale and use of ASRs, FDA did impose this one requirement on the LDTs sold by laboratories.

#### **IV. The IVDMIA Draft Guidance**

FDA's most significant action in the area of LDTs took place with regard to what it viewed as a new type of test category, which it referred to as In Vitro Diagnostic Multivariate Index Assays (IVDMIAAs). In 2006, FDA issued a draft guidance on IVDMIAs, which were, according to FDA, sophisticated tests that analyzed numerous different variables to establish a patient-specific result or "score" that was used for the diagnosis of a particular condition.<sup>33</sup> After receiving comments on the initial draft, it issued a revised version in July 2007.<sup>34</sup>

In the draft guidance, FDA stated it was concerned about the growth of IVDMIAs because it believed that the results of such tests would not be transparent to the ordering physician. According to FDA, such tests "are developed based on observed correlations between multivariate data and clinical outcome, such that the clinical validity of the claims is not transparent to patients, laboratorians and clinicians who order these tests. Additionally, IVDMIAs frequently have a high risk intended use."<sup>35</sup> According to FDA, patients who rely on IVDMIAs would be making critical decisions about their health care even though FDA had not ensured that the IVDMIA had been clinically validated and healthcare practitioners would be unable to clinically validate the test themselves.<sup>36</sup>

FDA gave, as an example of an IVDMIA, gene expression profiling assays for breast cancer prognosis, which analyze tumor tissue to determine the likelihood that a patient may have a recurrence, a factor useful in determining course of treatment.<sup>37</sup> The other examples were "a device that integrates quantitative results from multiple immunoassays to obtain a qualitative score that predicts a person's risk of developing a disease or condition," and "a device that integrates a patient's age, sex, and genotype of multiple genes to predict risk of or diagnose a disease or condition."<sup>38</sup>

In contrast, FDA noted it would not consider IVDMIAs to be tests where clinicians could easily interpret for themselves the results of the test, even if it combined multiple variables into a single patient's specific result. For example, according to FDA, standard maternal triple-screen testing was a test that would not be considered an IVDMIA because, according to FDA, clinicians had extensive experience in the use of such testing.<sup>39</sup> Similarly, simple genotype determinations would not be considered IVDMIAs, according to FDA, because even though multiple variables are measured, "the device does not incorporate a unique interpretation function but rather provides standard interpretation of the individual's variables that clinicians could do themselves."<sup>40</sup> Other examples of tests that would not be considered IVDMIAs were chromosomal copy number determinations, used to identify numerical changes in a patient's chromosomal DNA, and common clinical calculations, such as creatinine clearance,

cholesterol ratios or glomerular filtration rates, all of which were considered standard, commonly performed, interpretations.<sup>41</sup>

FDA took the position that it had jurisdiction over IVDMIAs because they would be considered devices under the FDCA. In its view, any laboratory developing an in-house test was a manufacturer of a medical device and thus subject to FDA jurisdiction under the act, although the agency had generally exercised enforcement discretion over such devices. It noted that IVDMIAs were simply a subset of LDTs; however, because of the particular concerns expressed, FDA had determined it would not exercise enforcement discretion over such tests.<sup>42</sup>

In the draft guidance, FDA stated that once it was issued in final form, FDA would not act for 12 months against entities that had IVDMIAs on the market at the time the guidance was issued. This would permit such companies a year to file for a 510(k) or PMA, whichever was appropriate. It would then continue to exercise enforcement discretion for an additional six months for those tests for which 510(k) or PMA had been filed during the one-year grace period.<sup>43</sup>

There were numerous comments filed on the IVDMIA Guidance, reflecting a variety of positions.<sup>44</sup> Commenters representing laboratories noted that it was not clear what types of tests would fall within FDA's definition, nor was it clear how laboratories would comply if they were subject to FDA's regulatory oversight. Furthermore, laboratories also noted that they were already regulated under CLIA, which, they argued, was more extensive than FDA's jurisdiction.<sup>45</sup> The Advanced Medical Technology Association (AdvaMed), which represents manufacturers, initially commented that the draft guidance represented "a significant change in policy" and urged more input from interested parties.<sup>46</sup> While its comments stated that most AdvaMed members believed that IVDMIAs should be subject to the same regulatory standards as other IVDs, it noted that some members believed that IVDMIAs were not medical devices and should only be regulated under CLIA.<sup>47</sup> In later comments, however, AdvaMed urged FDA to adopt a new model that would regulate all diagnostic tests, regardless of whether they were IVDs or test kits, based on the risk associated with their results.<sup>48</sup> The Genetics and Public Policy Center, at Johns Hopkins University, noted that FDA's current approach to regulating many genetic tests was "both incoherent and inadequate."<sup>49</sup> While it welcomed FDA's guidance as an "important first step," it also expressed concern that FDA was acting in a piecemeal fashion, rather than adopting a more "holistic" approach, focusing on all genetic tests.<sup>50</sup>

FDA reportedly considered issuing the IVD MIA Guidance at the end of George W. Bush's administration; however, nothing was published before the end of President Bush's term. Now, new leadership at FDA is reportedly reviewing the guidance and could issue it at some point in the future.

Although the IVD MIA Guidance is still in draft form, several companies have sought approval of IVD MIAs. In 2007, Agendia Corporation became the first company to obtain approval of an IVD MIA. Its MammaPrint test used molecular technology to predict whether existing cancer would metastasize and recur. FDA classified the test as Class II and established a new classification for gene expression profiling test systems for breast cancer prognosis.<sup>51</sup> In 2008, XDx Corporation obtained approval of its AlloMap test, which is used to determine whether a heart transplant patient is rejecting a new heart.<sup>52</sup> Finally, in September 2009, FDA approved another IVD MIA, the OVA1 test, which could detect ovarian cancer in certain pelvic masses. Based on the test results, a patient might be referred to an oncologist, even if other results were negative for ovarian cancer.<sup>53</sup> Thus, despite the questions that currently revolve around the draft guidance, FDA has begun to apply the principles set out there.

## **V. Other FDA Concerns**

In the wake of the IVD MIA Guidance, FDA has also begun to look more closely at LDTs in general. In a series of recent speeches, FDA officials have noted other questions exist related to the regulation of LDTs.<sup>54</sup> For example, at a conference sponsored by AdvaMed, Don St. Pierre, Deputy Director of FDA's Office of In Vitro Diagnostic Device Evaluation and Safety, noted that there was an uneven playing field for IVD manufacturers because distributed "test kits" had to go through FDA review prior to marketing, while LDTs did not.<sup>55</sup> His prepared presentation states that FDA is concerned about the potential for varying quality in laboratory test development and validation and because no postmarket reporting or recall requirements apply to LDTs.<sup>56</sup> The presentation also notes that FDA's view is that it has authority over LDTs and that all laboratories making LDTs are, in fact, medical device manufacturers.<sup>57</sup> It also notes that although FDA has applied enforcement discretion in this area, "just because you have a CLIA certificate, doesn't mean that you are not a medical device manufacturer and everything you do is under FDA enforcement discretion."<sup>58</sup> In addition, he noted that the policy of the agency had not changed, but "that it could," especially if patients were being put at risk.<sup>59</sup>

Most significant about the presentation was that it listed several types of tests that would not qualify as LDTs. These include the following:

- Distribution of tests between sites within an organization (e.g., within a corporate entity or coalition of labs);
- Contract manufactured tests;
- Custom manufactured devices;
- Tests obtained through agreements, purchase, from others;
- Non-laboratory services (software analysis, web tools, etc.).<sup>60</sup>

Although these bulleted items may not seem particularly controversial, in fact, they could raise significant questions with regard to FDA's regulation of LDTs. For example, the first bullet refers to "the distribution of tests between sites within an organization." Thus, FDA seems to be suggesting that if a laboratory properly developed an LDT within one facility, it could not transfer that test to, or share it with, another site within the same corporate entity. FDA's view seems to be that such action would result in commercial distribution of the LDT, although interestingly, FDA's regulations state that "commercial distribution" does not include "internal or interplant transfer of a device between establishments within the same parent, subsidiary, and/or affiliate company."<sup>61</sup> Nonetheless, if FDA held to this view, then it appears the second site would have to develop its own LDT "from scratch" without any interaction with the other site.

The second, third and fourth bullets all raise questions about situations where a laboratory uses an outside vendor to help it develop an LDT. For example, in some instances, a laboratory may develop the specifications for a test but then rely on a third-party vendor to help it develop the actual test kit that it uses. As with other LDTs, the laboratory may not intend to sell or distribute the test. It may plan to use the test only within its own facility and offer the test as its own proprietary testing service. Nonetheless, it appears that FDA may still believe that such arrangements raise questions of "commercialization," even though, when viewed in context, there may be little difference between the tests offered and a more traditional LDT.

The reference in the presentation to "custom manufactured devices" appears to be a reference to a specific type of LDT, microarray-based assays, which are commonly used in cytogenetics. Microarrays are sophisticated tests that are able to perform a large number of analyses of genetic material simultaneously. In the past, laboratories sometimes ordered these microarrays from outside manufacturers based on specifications developed by the laboratory. The laboratories would then offer these tests as LDTs, after they had been validated according to CLIA.<sup>62</sup> Recent reports have suggested that FDA is reviewing such tests, and may change

its approach of “regulatory discretion.”<sup>63</sup> According to these reports, meetings have occurred between interested parties and FDA. However, given the number and variety of microarrays, several experts have noted that if FDA were to regulate microarrays through the 510(k) or PMA processes, it could mean that many of these tests would no longer be available.<sup>64</sup> At the same time, at least one of the major manufacturers of these devices has announced that it will seek FDA clearance of its arrays.<sup>65</sup>

Mr. St. Pierre’s presentation also notes FDA’s concern about what the proper level of oversight should be and what type of clinical evidence should be required for such tests. In addition, it also expressed a concern about how to balance innovation and patient protection. He closed his presentation by reviewing the regulatory tools available to FDA. However, he finished with what may be the simplest—and most ominous—statement: “No matter what FDA does/does not do, someone is going to be unhappy.”<sup>66</sup>

## VI. Conclusion

Although LDTs have existed for decades, recent developments, especially in the area of genetic testing, has brought them increased attention. Although FDA has not yet taken any broad regulatory action, it has continued to scrutinize LDTs closely.

## Endnotes

1. The premarket notification procedure is commonly referred to as a “510(k)” notification, in reference to the statutory section from which it derives. *See* Federal Food, Drug, and Cosmetic Act (FDCA) § 510(k); 21 U.S.C. § 360(k).
2. In the past, these tests were also frequently referred to as “home brew” tests.
3. 42 U.S.C. § 263a.
4. FDA Rule on Analyte Specific Reagents, 62 Fed. Reg. 62,243, 62,249 (Nov. 21, 1997).
5. *Id.*
6. *See Draft Guidance for Industry, Clinical Laboratories, and FDA Staff, In Vitro Diagnostic Multivariate Index Assays* (July 26, 2007), at 2, *available at* [www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071455.htm](http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071455.htm) (hereinafter *IVDMIA Guidance*).
7. *See* 42 C.F.R. § 1, *et seq.*
8. *Id.* at § 493.801 *et seq.* A complete list of approved PT programs is *available at* [www.cms.hhs.gov/CLIA/downloads/ptlist.pdf](http://www.cms.hhs.gov/CLIA/downloads/ptlist.pdf).
9. 42 C.F.R. § 493.15.
10. *Id.* at § 493.1441 *et seq.*
11. *Id.* at § 493.1403, *et seq.*
12. *Id.* at § 493.17(c); *see also* [www.cms.hhs.gov/CLIA/10\\_Categorization\\_of\\_Tests.asp](http://www.cms.hhs.gov/CLIA/10_Categorization_of_Tests.asp).

13. 42 C.F.R. § 493.17(c)(4).
14. *Id.* at § 493.1258(b)(2).
15. CLIA Interpretive Guidelines, [www.cms.hhs.gov/CLIA/Downloads/apcsubk1.pdf](http://www.cms.hhs.gov/CLIA/Downloads/apcsubk1.pdf) at D5423.
16. 42 C.F.R. at § 493.1236.
17. Comments of American Clinical Laboratory Association (ACLA) on FDA's Draft Guidance on In Vitro Diagnostic Multivariate Index Assays, at 7 (Feb. 28, 2007), *available at* [www.clinical-labs.org/documents/IVDMIAcommentsfinal.pdf](http://www.clinical-labs.org/documents/IVDMIAcommentsfinal.pdf).
18. *Id.* at 2, n. 1.
19. Comments of ACLA on Genentech Citizen Petition (Dkt. FDA-2008-P-0638-001).
20. *See* <http://www.wlf.org/upload/Clinical%20Labs-%20FDA%20Citizen%20Petition.pdf>. The WLF petition was in response to FDA's IVDMIA Guidance, which is discussed in detail below.
21. *Id.* at 8, *et seq.*
22. *Id.* at 7.
23. Citizen Petition filed by Genentech, Inc., Dkt. No. FDA-2008-P-0638-001 (filed Dec. 8, 2008); *available at* <http://www.regulations.gov/search/Regs/home.html#documentDetail?R=09000064807d4a7e>.
24. *Id.* at 3.
25. *Id.* at 6, *et seq.*
26. *Id.* at 7, *et seq.*
27. Comments are *available at* [www.regulations.gov/search/Regs/home.html#docketDetail?F=FDA-2008-P-0638](http://www.regulations.gov/search/Regs/home.html#docketDetail?F=FDA-2008-P-0638).
28. "Laboratory Developed Test Oversight Should Be Strengthened," *available at* [www.cap.org/apps/cap.portal?\\_nfpb=true&cntvwrPtl\\_t\\_actionOverride=%2Fportlets%2FcontentViewer%2Fshow&\\_windowLabel=cntvwrPtl\\_t&cntvwrPtl\\_t%7BactionForm.contentReference%7D=statements%2Fidt\\_oversight\\_statement.html&\\_state=maximized&\\_pageLabel=cntvwr](http://www.cap.org/apps/cap.portal?_nfpb=true&cntvwrPtl_t_actionOverride=%2Fportlets%2FcontentViewer%2Fshow&_windowLabel=cntvwrPtl_t&cntvwrPtl_t%7BactionForm.contentReference%7D=statements%2Fidt_oversight_statement.html&_state=maximized&_pageLabel=cntvwr).
29. Letter from Steven Gutman, Director, OIVD, FDA to Peter J. Levine, President & CEO, Correlogic Systems, Inc. (July 12, 2004).
30. Letter from Peter J. Levine, President and CEO, Correlogic, to Steven Gutman, FDA, (July 14, 2004) *available at* <http://www.correlogic.com/pdfs/July14SteveGutmanLetter.pdf>.
31. Letter to David P. King, President & CEO, LabCorp, from Steven Gutman, Director, OIVD, FDA (Sept. 29, 2008), *available at* [www.fda.gov/ICECI/EnforcementActions/WarningLetters/2008/ucm1048114.htm](http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2008/ucm1048114.htm).
32. 21 C.F.R. § 809.30(e).

33. The original guidance was published in September 2006. *See* 71 Fed. Reg. at 52,800 (Sept. 7, 2006). This first version of the guidance is *available at* [www.fda.gov/OHRMS/Dockets/98fr/06d-0347-gdL0001.pdf](http://www.fda.gov/OHRMS/Dockets/98fr/06d-0347-gdL0001.pdf).
34. *See Draft Guidance for Industry, Clinical Laboratories, and FDA Staff, IVDMIA Guidance* (July 26, 2007), at 2, *available at* [www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071455.htm](http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071455.htm).
35. IVDMIA Guidance at 4.
36. *Id.*
37. *Id.* at 5. This was clearly a reference to two tests, Genomic Health’s OncotypeDx test and Agendia’s MammaPrint test. For more information, *see* [www.genomichealth.com/OncotypeDx/Index.aspx](http://www.genomichealth.com/OncotypeDx/Index.aspx); and [www.agendia.com/pages/mammaprint/21.php](http://www.agendia.com/pages/mammaprint/21.php) (last visited Dec. 12, 2009).
38. *Id.* at 6.
39. *Id.*
40. *Id.*
41. *Id.*
42. *Id.* at 4.
43. *Id.* at 10.
44. For a good summary of comments submitted, *see* “Selected Annotated List of Comments to FDA’s Sept. 2006 Draft IVDMIA Guidance Document, Compiled by Genetics and Public Policy Center,” *available at* [www.dnapolicy.org/resources/FDAIVDMIAComentchart.pdf](http://www.dnapolicy.org/resources/FDAIVDMIAComentchart.pdf).
45. Comments of the American Clinical Laboratory Association, *available at* [www.clinical-labs.org/documents/ACLAComentstoFDAonIVDMIAREvisedDraftGuidance.pdf](http://www.clinical-labs.org/documents/ACLAComentstoFDAonIVDMIAREvisedDraftGuidance.pdf).
46. Comments of Carolyn Jones, Assoc. Vice President, AdvaMed to FDA at 2 (Feb. 8, 2007), *available at* [www.fda.gov/ohrms/dockets/dockets/06d0347/06D-0347-EC78-Attach-1.pdf](http://www.fda.gov/ohrms/dockets/dockets/06d0347/06D-0347-EC78-Attach-1.pdf).
47. *Id.* at 1-2.
48. Letter to D.G. Schultz, Director, CDRH, FDA, from Khatereh Calleja, Assoc. Vice-Pres., AdvaMed (Mar. 27, 2009).
49. K. Hudson and G. Javitt, Comments of Genetics and Public Policy Center (Mar. 5, 2007), *available at* <http://www.regulations.gov/search/Regs/home.html#documentDetail?R=0900006480456640>.
50. *Id.* at 3.
51. 21 C.F.R. § 866.6040.
52. “FDA Clears Test to Help Doctors Manage Heart Transplant Patients,” [www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/UCM116939.htm](http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/UCM116939.htm).

53. “FDA Clears a Test for Ovarian Cancer, Test can help identify potential malignancies, guide surgical decisions,” [www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/UCM182057.htm](http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/UCM182057.htm).
54. “Under New Leadership, FDA Diagnostics Office to Tighten Its Control,” *THE GRAY SHEET* (July 27, 2009); “Lab-developed Tests Will be Regulated, Guidance Coming: FDA,” FDA Webview (Sept. 15, 2009).
55. Don St. Pierre, “FDA Regulation of Testing; FDA Oversight—Where Are We,” Presentation to Washington G-2 Reports, Lab Institute (Sept. 24, 2009) (author’s files) (hereinafter St. Pierre presentation).
56. *Id.* at slide 8.
57. *Id.* at slide 9.
58. *Id.*
59. *Id.* at slide 10.
60. *Id.* at slide 11.
61. 21 C.F.R. § 807.2(b)(1).
62. See, *FDA May Increase Oversight Over Array-Based Clinical Cytogenetic Tests*, *BIOARRAY NEWS*, Oct. 13, 2009, available at <http://www.genomeweb.com/arrays/fda-may-increase-oversight-over-array-based-clinical-cytogenetic-tests>.
63. *Id.*
64. *Id.*
65. *Illumina to Submit Cytogenetics Package to FDA, Commits to Using Arrays in Dx*, *BIOARRAY NEWS*, Jan. 26, 2010, available at <http://www.genomeweb.com/arrays/illumina-submit-cytogenetics-package-fda-commits-using-arrays-dx>.
66. St Pierre Presentation, at slide 14.

