Genentech
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Division of Dockets Management
US Food and Drug Administration (FDA)
Department of Health and Human Services
5630 Fishers Lane
Room 1061
Rockville, MD 20852

December 5, 2008

Dear Sir or Madam:

Genentech submits the attached Citizen Petition under Sections 201, 301, 510, 513, 519, and 520 of the Food, Drug, and Cosmetic Act and 21 Code of Federal Regulations Section 10.30 to request the Commissioner of Food and Drugs require all *in vitro* diagnostic tests intended for use in drug or biologic therapeutic decision making be held to the same scientific and regulatory standards. These scientific and regulatory standards should apply regardless of whether the *in vitro* diagnostic tests are developed and sold by device manufacturers as diagnostic test "kits" or are developed in-house by laboratory-based companies for in-house testing ("laboratory-developed tests" or "LDTs").

Respectfully submitted,

Sean Johnston

Sean A. Johnston
Senior Vice President and General Counsel

cc: Michael O. Leavitt, Secretary of DHHS
Andrew C. von Eschenbach, MD, Commissioner of Food and Drugs
Gerald F. Masoudi, Chief Counsel, FDA
Janet Woodcock, MD, Director, Center for Drug Evaluation and Research, FDA
Daniel G. Schultz, MD, Director, Center for Devices and Radiological Health, FDA

FDA-2008-P-0638 CP

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Genentech, Inc. Citizen Petition

Regulation of *In Vitro* Diagnostic Tests

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I. EXECUTIVE SUMMARY AND ACTION REQUESTED

Genentech, Inc. ("Genentech") submits this petition to the United States Food and Drug Administration ("FDA" or the "Agency") under 21 Code of Federal Regulations ("CFR") § 10.30, and sections 201, 301, 510, 513, 519, and 520 of the Federal Food, Drug, and Cosmetic Act ("FDCA") to request the Commissioner of Food and Drugs require all *in vitro* diagnostic tests intended for use in drug or biologic therapeutic decision making be held to the same scientific and regulatory standards, regardless of whether the tests are developed and sold by device manufacturers as diagnostic test "kits"[1] or are developed by clinical laboratory companies for in-house testing ("laboratory-developed tests" or "LDTs"[2]). Currently, FDA regulates *in vitro* diagnostic tests in kit form, but not LDTs. Given the potential risks to patient safety associated with use of diagnostic tests that make unsubstantiated claims intended to guide specific drug or biologic therapeutic decision making, it is imperative that FDA exercise its regulatory authority consistently over all *in vitro* diagnostic test products, including LDTs, to ensure that claims made for the tests are scientifically proven. Failure to do so could present safety risks for patients as more treatment decisions are based in whole or in part on the claims made by such test makers.

Genentech believes that FDA should exercise its regulatory authority over all *in vitro* diagnostic tests pursuant to the risk-based classification system it uses for medical devices. Based on the current classification system, Genentech anticipates that many LDTs will be considered low risk and would not require significant regulatory oversight. That would allow FDA to focus its attention on high risk LDTs, which are those that are used in clinical decision making to determine the use of a particular drug or biologic for the treatment of a patient. The use of such high risk tests, if based on scientific claims made but not adequately validated, could place patients at risk either for receiving the wrong treatment (thus exposing them to unnecessary side effects or possible treatment failure), or for not receiving appropriate therapy.

To be clear, Genentech fully supports the development of LDTs and other diagnostic tests that help inform clinical practice, and recognizes the important role they can play in

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[1] An *in vitro* diagnostic test "kit" is an *in vitro* diagnostic product (defined at 21 CFR § 809.3) made up of specified products, such as collection devices, reagents, instrumentation, or systems, that is reviewed by FDA under a Premarket Approval Application under FDCA § 513 or a Premarket Notification under FDCA § 510(k). The term "kit" has no specific regulatory definition; however, it is well-understood by FDA and *in vitro* diagnostic companies. *See, e.g., FDA, Guideline for the Manufacture of In Vitro Diagnostic Products*, at 19-22 (January 10, 1994), *available at* http://www.fda.gov/cdrh/comp/918.pdf; *510(k) Summary for VITROS Chemistry Products Calibrator Kit (*December 9, 2004), *available at* http://www.fda.gov/cdrh/pdf4/K042838.pdf (use of the word "kit" in regulatory document).

[2] A "laboratory developed test" is a test developed by a clinical laboratory for use only by that laboratory. It can be made out of general purpose reagents or analyte specific reagents ("ASRs") or a combination of the two. Another term used for an LDT is a "home brew" assay, which usually implies that the FDA has not cleared or approved the test. Some LDTs that do not use ASRs are commonly referred to as "home brew-home brew tests" meaning an LDT using general purpose reagents and/or laboratory-developed ASRs.

modern medicine. As FDA is aware, Genentech is a pioneer in the development of targeted therapies, most notably with our breast cancer therapy Herceptin® (trastuzumab), which targets tumors that over-express HER2 protein. Genentech strives to be a leader in developing diagnostics that can identify appropriate patients for our novel, targeted treatments. We also believe diagnostics are the key to efficient and effective drug development and to ensure that the right drug reaches the right patient. To that end, Genentech is applying a personalized medicine approach to nearly all of its clinical development programs and is developing diagnostic approaches with every product we believe is an appropriate candidate for such an approach. We collaborate with a variety of possible partners in these efforts, including traditional diagnostic test kit manufacturers as well as clinical laboratories. We believe it is critical that the regulation of diagnostic tests remain neutral to the nature of the entity that makes and markets the test and focus instead on the claims being made about the test by the diagnostics maker, with particular attention paid to claims that are intended to guide therapeutic decision making. Genentech is not suggesting that high risk LDTs are inherently unsafe or necessarily place patients at a greater health risk than diagnostic test kits, nor are we advocating regulation that would unduly restrict access to beneficial diagnostic information. Rather, Genentech believes that all claims made regarding LDTs and other diagnostic tests should be scientifically validated and approved by FDA to ensure that health care providers and patients have access to consistently and appropriately validated diagnostics to help guide their decision making.

To accomplish this goal, Genentech respectfully requests that FDA initiate rulemaking to exercise regulatory jurisdiction over all LDTs, and use its current risk-based classification system to determine the level of regulatory oversight and review that is necessary and appropriate for these tests.[3] Genentech also requests that FDA concurrently initiate appropriate enforcement action, pursuant to its existing authority, against any clinical laboratory or other company that is selling an LDT and making claims about its potential indication for use, effectiveness or value, or that otherwise impacts patient safety without having sufficient analytical and clinical evidence to support such claims.[4] Together, these

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[3] Genentech's view is consistent with recommendations made in the Secretarial Advisory Committee on Genomics, Health, and Society ("SACGHS") report, *U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services*, (April 2008), *available at* http://www4.od.nih.gov/oba/SACGHS/reports/SACGHS_oversight_report.pdf (hereinafter "SACGHS Oversight Report"). *See* SACGHS Oversight Report at 1 ("To help close the gaps in oversight related to clinical validity, which would help assure the appropriate use of laboratory tests, the Food and Drug Administration (FDA) should address all laboratory tests, regardless of how they are produced (*i.e.*, as a commercial test kit or laboratory-developed test), in a manner that takes advantage of its current experience."); *see also id.* at 8 and 112 (recommending that "FDA should address all laboratory tests in a manner that takes advantage of its current experience in evaluating laboratory tests," as well as the development of "criteria for risk stratification and a process for systematically applying these criteria").

[4] Genentech's request is consistent with the SACGHS Oversight Report's recommendation that, "[a]ppropriate Federal agencies, including...FDA...should strengthen monitoring and enforcement efforts against laboratories and companies that make false and misleading claims about laboratory tests...." *Id.* at 9 and 113; *see also id.* at 51 (noting "[i]nsufficient monitoring and enforcement of laws pertaining to false and misleading claims about genetic tests" as a gap in genetic testing oversight).

measures will enhance and ensure the safety of patients whose medical therapies depend on diagnostic tests of proven analytical and clinical validity.

Given the recent proliferation and availability of diagnostic tests that make unsubstantiated, and therefore possibly inaccurate or misleading, claims intending to guide both the treatment and payment decisions made by health care providers and payers, Genentech believes it is critical for FDA to assert its jurisdiction over all such tests, and to provide much needed clarity over its ability and intention to regulate LDTs. The FDA took a step in that direction in issuing the FDA draft guidance on *In Vitro* Diagnostic Multivariate Index Assays ("IVDMIAs"). However, Genentech would like FDA to expand and strengthen its regulatory oversight over other LDTs. The failure to apply clear and consistent standards and regulatory oversight to all LDTs could threaten the public health and serve as a disincentive for the development of diagnostic test kits through FDA's review pathway, thereby potentially undermining the move toward more personalized approaches to health care treatment and delivery.

To this end, Genentech's Citizen Petition:

1) Substantiates several patient-focused reasons why all diagnostic tests should be held to the same scientific and regulatory review standards;
2) Establishes through case law, regulatory precedent, and examples, FDA's statutory authority and regulatory jurisdiction over all LDTs; and
3) Requests that FDA establish regulations governing all LDTs, and take appropriate enforcement action as rulemaking progresses against any clinical laboratory or other company that is selling an LDT and making claims about its potential indication for use, effectiveness or value, or that otherwise impacts patient safety without having sufficient scientific or clinical evidence to support such claims.

II. BACKGROUND

Physicians have long used *in vitro* diagnostic tests as an integral part of their medical decision making. The majority of such *in vitro* diagnostic tests are in diagnostic test kit form and are regulated by FDA as medical devices, and most are sold only after a pre-market application has been "cleared" under FDCA § 510(k) or "approved" under FDCA § 513. The remainder are LDTs which are developed and performed in individual clinical laboratories, historically for rare diseases or other uncommon conditions, but now for a wide and growing list of common conditions, some serious and life-threatening.

Until recently, few *in vitro* diagnostic tests were available that tied the administration of a particular drug or biologic therapy to that test. Rather, *in vitro* diagnostic tests were more commonly used for monitoring purposes, or as an aid to a physician's assessment of whether a patient had a particular condition. Typically these tests were not used to determine which particular drug or biologic the patient should be given. Over the past several years, however, the situation has evolved rapidly, due in part to scientific advances, industry efforts to improve drug and biologic therapy, and FDA's Critical Path initiative, which encourages the development of biomarkers that can be used both to speed drug development and to define

more precisely which patients should use a particular therapy.[5] This effort to tailor drug or biologic therapy for an individual patient ("personalized medicine") has begun to bear fruit. At present, pharmacogenomic information is contained in the labeling of approximately 10 percent of all FDA-approved drugs and for several drugs, including Genentech's targeted breast cancer therapy, Herceptin® (trastuzumab), which requires that the patient be tested for a particular genetic characteristic and the results considered before drug administration.[6] Because the future of personalized medicine depends on the development of pharmacogenomic tests, it is critical that they are accurate, reliable, and clinically valid (*i.e.*, effective).

III. FDA OVERSIGHT OF LDTS IS NECESSARY TO ENSURE REGULATORY CONSISTENCY AND PROTECT THE PUBLIC HEALTH

The availability of LDTs designed to assist physicians in making decisions regarding which therapies to prescribe to patients is increasing. The clinical laboratories and their associated companies that market them make clinical claims about the purpose (*i.e.*, intended use) and validity of their LDTs, but since such claims are rarely submitted to FDA for review, it is simply unknown whether they are supported by sufficient analytical and clinical evidence. The potential risks to patients when treatment decisions are based on LDTs that lack analytical or clinical validity are not adequately addressed by the Clinical Laboratory Improvement Amendments ("CLIA") or voluntary oversight.[7] Although we recognize that FDA is not able to take enforcement action against each violation of FDCA and that it has discretion to determine how best to allocate its scarce resources (*Heckler v. Chaney*, 470 U.S. 821, 831-32 (1985)), compelling reasons exist as to why FDA should take a stronger regulatory stance with respect to LDTs.

A. The Number and Types of LDTs is Increasing

The number and type of LDTs available to health care providers and payers has grown significantly in recent years.[8] In a March 2007 comment to FDA, the law firm Hyman, Phelps &

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[5] *See FDA, Critical Path Opportunities Report* (March 2006), *available at* http://www.fda.gov/oc/initiatives/criticalpath/reports/opp_report.pdf.

[6] Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels, http://www.fda.gov/cder/genomics/genomic_biomarkers_table.htm (last visited November 17, 2008).

[7] While CLIA establishes certain laboratory standards, *e.g.*, for personnel, certification, quality assurance and quality control, it provides limited standards for assessment of analytical validity and virtually no standards for the assessment of clinical validity. *See* 42 CFR Part 493. Voluntary professional organizations do significant work in this field, but they have no enforcement authority and thus offer limited public health protection.

[8] In a 1995 survey conducted on behalf of the Task Force on Genetic Testing that was created by the National Institutes of Health (NIH), Department of Energy, and the Working Group on Ethical, Legal, and Social Implications of Human Genome Research, there were at least 53 biotechnology companies and 212 non-profit laboratories offering genetic testing. *Final Report of the Task Force on Genetic Testing, App. 3: State of the Art of Genetic Testing in the United States: Survey of Biotechnology Companies and Nonprofit Clinical Laboratories and Interviews of Selected Organizations*, at 102 (September 1997), *available at* www.genome.gov/100001733. By 1997, over 500 commercial, university, and health department laboratories provided tests for inherited and

McNamara, PC stated that it was aware of approximately 200 LDTs on the market or under development that might be considered IVDMIAs.[9] As drug and biologic manufacturers continue to search for diagnostics to identify the precise patient population for which a therapy is appropriate, clinical laboratories are beginning to fill the need traditionally met by diagnostic test kit manufacturers because they have a lower regulatory burden and a more favorable reimbursement environment. While Genentech welcomes the availability of LDTs as a possible alternative to diagnostic kits, FDA's regulatory approach to diagnostics must adapt to reflect the increasing shift of assay development from kits to LDTs and to the increasing number of LDTs that are being marketed and used to make treatment and reimbursement decisions. Given that clinical laboratories are now developing and selling many of the same types of diagnostic tests traditionally manufactured as diagnostic test kits – including novel test systems used to make critical health care decisions – it is important that FDA apply the same standards regarding proof of safety and effectiveness to all diagnostic tests, regardless of which type of entity is manufacturing them.

Examples of Unapproved LDTs Used with Genentech Products

Below are some examples of LDT manufacturers making claims about their test(s), without FDA approval, for Genentech products (without collaboration or consultation with Genentech). Although this is a small sample of the LDTs that are being developed outside of FDA's review, Genentech believes that these examples demonstrate the extent to which LDTs are being marketed and used to guide patient treatment decisions, without FDA review and without any assurance that the claims being made about these tests are analytically or clinically valid.

Herceptin® (Trastuzumab)

An increasing number of LDTs, of unknown analytical and clinical validity, are marketed or are in development for use to determine whether a patient should be treated with Herceptin, Genentech's therapy for HER2-positive breast cancer. Herceptin's FDA-approved label states that "[d]etection of HER2 protein overexpression is necessary for selection of patients appropriate for Herceptin therapy because these are the only patients studied and for whom benefit has been shown."[10]

The Herceptin label further provides information on several FDA-approved commercial assays (medical device kits) that can be used to aid in the selection of patients appropriate for

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chromosomal disorders and genetic predispositions in the United States. *Id. at* 7. According to a web site funded by the NIH and maintained by the University of Washington, Seattle, Washington, as of November 15, 2008, there were 597 laboratories, testing for 1,364 clinical diseases or conditions, http://www.genetests.org (last visited November 19, 2008).

[9] Comment to Docket 2006P-0402: Washington Legal Foundation Citizen Petition, at 22 (March 23, 2007), *available at* http://www.fda.gov/ohrms/dockets/dockets/06p0402/06P-0402-EC2-Attach-1.pdf.

[10] Herceptin® (trastuzumab) Full Prescribing Information, Genentech, Inc., May 2008, Section 5.5.

Herceptin therapy. These include HercepTest™ and Pathway® HER-2/new (immunochemistry ("ICH") assays) and PathVysion® and pharmDx™ (fluorescence in-situ hybridization ("FISH") assays).[11] The Herceptin label does not provide information on any non-approved LDTs for selecting patients for Herceptin therapy; however, we are aware that there are clinical laboratories that market and perform HER-2 assays as LDTs, for the purpose of selecting patients for Herceptin therapy, using novel technologies not yet approved or cleared by FDA. Specifically, in February 2008, CombiMatrix Corporation's subsidiary, CombiMatrix Molecular Diagnostics, launched an LDT to detect amplification of the HER-2 gene in early breast cancer called the HerScan test.[12] In a press release, the company states:

> The HerScan test is designed to give pathologists and oncologists an objective measure of HER2 gene copy number with simultaneous analysis of the entire tumor genome. As a function of the enumeration of the HER2 gene through the HerScan test, patients are assigned to one of four categories of HER2 gene status: Amplification, Gain, Normal, or Loss.[13]

In addition, Monogram Biosciences, Inc. ("Monogram") sells its HERmark™ Breast Cancer Assay for HER-2 protein expression. Monogram's claims about that assay include the following:

> **Direct measure of the levels of HER2 total protein and its activated form, the HER2 homodimer - trastuzumab's target**
>
> - 15-20% of patients identified by conventional technologies as HER2 Negative expected to be reclassified by HERmark.
> - Highly sensitive, detects HER2 levels from 2,500 to over 1 million receptors per cell (7 - 10x more sensitive than IHC).
> - HERmark quantification of HER2 levels provides additional confidence for trastuzumab response.
> - Current HERmark clinical data suggests correlation to therapy response in metastatic breast cancer.[14]

However, no information on FDA's web site indicates that FDA has reviewed the CombiMatrix or Monogram LDTs, despite the claims regarding clinical validity made by both companies. Monogram's web site states that its HERmark assay is a "CLIA validated assay processed at Monogram Sciences a CAP-certified central laboratory".[15] During Monogram's Q4 2007 earnings call, the company stated: "Starting from clinical studies to regulatory status,

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[11] *Id.*

[12] *CombiMatrix Molecular Diagnostics Announces the Validation and Launch of the HerScan Test for Assessment of Newly Diagnosed Breast Cancer* (February 26, 2008), http://investor.combimatrix.com/releasedetail.cfm?ReleaseID=296042.

[13] *Id.*

[14] http://hermarkassay.com (last visited November 15, 2008) (emphasis in original).

[15] http://hermarkassay.com/hermark_features.aspx (last visited November 15, 2008).

the HERmark assay is fully approved."[16] Based on these statements, Monogram seems to mean that the College of American Pathologists ("CAP") has certified that the central laboratory has met all applicable standards for CAP accreditation, and that the laboratory has complied with CLIA's method validation requirements for LDTs, not that the assay is "fully-approved" by FDA.

Genentech is concerned that this type of a claim may confuse physicians and patients and lead them to believe that the assay has been validated and approved for use by FDA. As a consequence, treatment and payment decisions may be made based on faulty assumptions and unvalidated claims. Monogram claims that its test is more accurate and reproducible than current methods, but to our knowledge, no independent verification of that statement exists.[17] The number of patients who might be assessed using this unapproved LDT is significant – Monogram estimates that approximately 60,000 women are candidates for testing with its assay.[18]

Rituxan® (Rituximab)

In January 2007, Clinical Data launched its PGxPredict™:RITUXIMAB, a pharmacogenomic test that Clinical Data claims can be used to predict the likelihood of response to Rituxan by patients with follicular non-Hodgkin's lymphoma.[19] This LDT is performed in a laboratory that is a subsidiary of Clinical Data.[20] In its January 30, 2007 press release announcing that test, Clinical Data stated:

> PGxPredict:RITUXIMAB is a pharmacogenetic test that helps physicians predict the likelihood of a given patient responding to rituximab monotherapy in the treatment of follicular non-Hodgkin's lymphoma (NHL). This test allows oncologists to identify whether a patient is among the 20% of people that will demonstrate a stronger likelihood of responding to rituximab. . . . 'We are very pleased and excited that we can bring pharmacogenetic tests like these to market rapidly and provide physicians with more information when making important clinical decisions with their patients. . . . For the first time in this life-threatening disease, physicians can consider the genetic makeup of each patient in evaluating the likelihood of response to rituximab. Having this information will assist physicians when considering treatment options.' . . . Based on this published data,

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[16] Monogram Biosciences, Inc. Q4 2007 Earnings Call Transcript at 3 (February 7, 2008), http://seekingalpha.com/article/64947-monogram-biosciences-inc-q4-2007-earnings-call-transcript.

[17] *See, e.g.*, Press releases, *Monogram Announces 2008 First Quarter Financial Results* (May 1, 2008), http://ir.monogrambio.com/releasedetail.cfm?ReleaseID=307849; *Monogram and Dana-Farber Cancer Institute Initiate Evaluation of HERmark(TM) Breast Cancer Assay in Metastatic Breast Cancer* (September, 23, 2008), http://ir.monogrambio.com/releasedetail.cfm?ReleaseID=336196.

[18] Monogram Biosciences, Inc. Q4 2007 Earnings Call Transcript, at 4 (February 7, 2008), http://seekingalpha.com/article/64947-monogram-biosciences-inc-q4-2007-earnings-call-transcript.

[19] *Clinical Data Launches PGxPredict™:RITUXIMAB on Schedule* (January 30, 2007), http://investor.clda.com/releasedetail.cfm?releaseid=227577.

[20] The test can be ordered through the Clinical Data subsidiary PGxHealth, http://www.pgxhealth.com/genetictests/order.cfm (last visited May 3, 2008).

approximately 20% of patients will carry the 158V/V variant and will be identified by the PGxPredict:RITUXIMAB test as more likely to respond (estimated response rate of 90%). Approximately half of those who do not carry the 158V/V variant may still respond to rituximab monotherapy. The assay will detect the variant with over 99% accuracy, based on the method validation performed by the testing laboratory, Cogenics, Inc., a subsidiary of Clinical Data.

While rituximab has proven to be valuable in the treatment of patients with follicular, CD20-positive NHL, its high cost of approximately $12,000 for four weekly treatments, and risk of toxicity may make the choice to prescribe or maintain therapy with rituximab a difficult one for physicians and patients, especially with other treatment options available. The PGxPredict:RITUXIMAB test will provide unique and valuable information to physicians and patients as they evaluate their treatment options.[21]

Similarly, Clinical Data claims on its web site:

PGxPredict™:RITUXIMAB Test - Opening the door to new information for patients and physicians in the treatment of non-Hodgkin's lymphoma.

Rituximab is an immunotherapeutic agent indicated for the treatment of follicular, CD20-positive B-cell non-Hodgkin's lymphoma. Rituximab monotherapy has been shown to be effective only in up to 57% of cases, and can cause serious side effects, some of which could be life-threatening. Side effects and the drug's cost may make rituximab a difficult choice for many practitioners and patients.

The **PGxPredict:RITUXIMAB** test is changing the rules, making it possible to provide patients and physicians with specific information about the likelihood of response to rituximab monotherapy.[22]

In the absence of independent review of Clinical Data's claims on the accuracy of the test, there is no certainty that the "specific information" offered to physicians on rituximab monotherapy is accurate or useful to the physician. We are concerned that these clinically unvalidated claims may result in inappropriate use of Rituxan as a therapy.

Avastin® (Bevacizumab)

Rosetta Genomics is a company that is developing a "full range of microRNA-based diagnostic and therapeutic tools, focusing primarily on cancer and various women's health indications." According to its April 3, 2008 press release, the Rosetta Genomics test for classification of non-small cell lung cancer ("NSCLC") (squamous or non-squamous), will be made available through Columbia University Medical Center's licensed high complexity molecular pathology laboratory.[23] There is no indication on the Rosetta Genomics web site

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[21] *Supra* note 19.

[22] http://www.pgxhealth.com/genetictests/rituximab (last visited October. 8, 2008) (emphasis in original; footnotes omitted).

[23] *Columbia University Medical Center and Rosetta Genomics Announce Columbia University's Submission of the First Cancer Diagnostic Test Based on Rosetta Genomics Proprietary MicroRNA Technology for Approval to the New York State Department of Health* (April 3, 2008), http://phx.corporate-ir.net/phoenix.zhtml?c=203066&p=irol-

that it intends to seek FDA review of this test. In this press release, Rosetta Genomics claims that the test accurately differentiates squamous from non-squamous NSCLC and can be used to guide treatment decisions with respect to Avastin:

> The ability of physicians to accurately differentiate squamous (scalelike) from non-squamous NSCLC is an important treatment guide. Bevacizumab, an angiogenesis inhibitor and an important new modality of therapy for non-squamous NSCLC, includes a black-box warning about substantially higher rates of severe or fatal hemorrhage among patients with squamous NSCLC histology compared with non-squamous NSCLC.
>
> Currently, an estimated 60,000 patients per year are potential candidates for targeted therapy with Avastin(TM), a market available angiogenesis inhibitor, in the United States.[24]

On its web site, Rosetta Genomics further explains what it perceives to be the value of its test, referring to Avastin as "a recently approved angiogenesis inhibitor for NSCLC" rather than by name:

> Differentiating squamous from non squamous cell lung cancer presents a challenge to physicians, but until recently this differentiation was not particularly relevant from a therapeutic or prognostic standpoint. This is due to the fact that no drug was designed for a specific NSCLC sub-type.
>
> However, the advent of targeted lung cancer therapies directed at specific cellular alterations now demands the most accurate classification possible for non-small cell lung carcinomas.
>
> A recently approved angiogenesis inhibitor for NSCLC has been shown to have severe side effect for squamous-cell lung cancer patients. Furthermore, this targeted therapy includes a black-box warning about substantially higher rates of severe or fatal hemorrhage among patients with squamous NSCLC histology compared with non-squamous NSCLC. This has led patients with squamous-cell histology to be regarded by many as inappropriate candidates for therapy with this drug. In addition, several other targeted drugs for NSCLC currently under development may require this type of sensitive differentiation due to different side effect profile or different levels of efficacy.
>
> Currently, an estimated 60,000 patients per year in the United States are potential candidates for targeted therapy with market available angiogenesis inhibitor.
>
> Combining Rosetta Genomics' proprietary microRNA extraction technology from FFPE samples with our sensitive quantification platforms, and microRNA molecular biomarkers identified by Rosetta Genomics, Columbia University Medical Center's (CUMC) High Complexity Molecular Pathology Laboratory has developed a test which identifies

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newsArticle&ID=1125240&highlight. However on July 24, 2008, Rosetta Genomics announced that it acquired Parkway Clinical Laboratories, a privately-held CLIA-certified lab. *Rosetta Genomics Completes Acquisition of Parkway Clinical Laboratories Inc.* (July 24, 2008), http://phx.corporate-ir.net/phoenix.zhtml?c=203066&p=irol-newsArticle&ID=1178656&highlight=.

[24] April 3, 2008 press release, *supra* note 23.

> squamous cell carcinoma of the lung with **sensitivity** of **96 percent** and **specificity** of **90 percent**.
>
> This is the first test utilizing microRNAs' unique sensitivity and specificity as biomarkers that may offer a standardized and objective method for cancer classification. The test is now approved for clinical use nationwide through CUMC's High Complexity Molecular Pathology Laboratory. [25]

As with the other LDTs mentioned, no independent verification has been made of these claims, and thus there is no way to be certain that the information offered to physicians is accurate and reliable and sufficient to support therapeutic decisions.

Tarceva® (Erlotinib)

Tarceva targets the epidermal growth factor receptor ("EGFR") and is approved for use in the treatment of locally advanced and metastatic NSCLC after failure of at least one prior chemotherapy regimen and in combination with gemcitabine for the first-line treatment of patients with locally advanced, unresectable, or metastatic pancreatic cancer. There are studies suggesting that mutations of EGFR and K-ras gene ("KRAS") may affect the effectiveness of drugs such as Tarceva in lung cancer. Tests for such mutations are being sold as LDTs by Genzyme Genetics to guide treatment decisions for patients with NSCLC.[26] The Genzyme Genetics web site states:

> Genzyme's KRAS Mutation Analysis provides additional guidance in therapeutic treatment decisions for patients with colorectal cancer (CRC) and non-small cell lung cancer (NSCLC). . . . Mutations in the KRAS gene, a known downstream signaling molecule in the EGFR signaling pathway, have been described in approximately 30-50% of colorectal carcinomas and approximately 15-30% of lung adenocarcinomas.
>
> Recent studies have found mutations in the KRAS gene to be associated with a poor prognosis. Studies have also found KRAS mutations more frequent in patients who show limited clinical response to targeted anti-epidermal growth factor receptor (anti-EGFR) therapies. As a result, determining the KRAS mutational status of a tumor may guide therapeutic decision making for patients with CRC and NSCLC.[27]

In another section of the Genzyme web site ("Enhancing Personalized Medicine in Cancer"), it refers to its "advanced menu of testing services to help doctors diagnose and effectively treat patients with cancer."[28] Specifically, under the heading "Genzyme Genetics: Personalized Medicine Cancer Testing Overview," it refers to three of its tests for patients with NSCLC

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[25] http://www.rosettagenomics.com/inner.asp?first_tier=24&second_tier=103&third_tier=88 (last visited October 8, 2008) (emphasis in original).

[26] *See* Genzyme Genetics web site, http://www.genzymegenetics.com/testmenu/tests/cancer/gene_p_testmenu_can_test_kras.asp (last visited October 20, 2008).

[27] *Id.*

[28] http://www.genzyme.com/corp/media/PersonalizedMedicine_FactSheet.pdf (last visited October, 20, 2008).

(EGFR Amplification, EGFR Mutation Analysis, and KRAS Mutation Analysis) for use when prescribing Tarceva.[29]

Response Genetics, Inc. is engaged in the research and development of pharmacogenomic cancer diagnostic tests. The company currently offers tests through a CLIA-certified laboratory. In a March 5, 2008 press release, Response Genetics announced:

> that its ResponseDX: Lung(TM) and ResponseDX: Colon(TM) tests are now available to select medical institutions and practice groups through its CLIA-registered laboratory. ResponseDX: Lung(TM) and ResponseDX: Colon(TM) are PCR-based tests that help guide therapeutic treatment decisions in patients with non-small lung cancer (NSCLC) and colorectal cancer (CRC).[30]

The press release further stated that Response Genetics is providing the tests to help determine response to erlotinib (Genentech's Tarceva), and to other drugs including gefitinib, gemcitamine, and fluoropyrimidine-based therapies.[31]

B. Potential Health and Safety Concerns with LDTs

The FDA has similarly identified the concerns Genentech has expressed. Specifically, FDA recognizes that an *in vitro* diagnostic test that is used to make a critical health care decision is a high risk device.[32] The FDA has emphasized repeatedly, particularly for high risk devices, that it is critical to the safety of a patient that an assay provide a correct result that is clinically meaningful.

Recently, FDA has shown a willingness to regulate some high risk LDTs based on concerns about patient safety. By letter dated August 7, 2008, FDA informed Laboratory Corporation of America ("LabCorp") that the Agency wanted to discuss LabCorp's marketing of the Ovasure™ Yale Ovarian Cancer Test which is intended to identify high-risk women who might have ovarian cancer.[33] The FDA's letter to LabCorp stated "[w]e believe that you are offering a high risk test that has not yet received adequate clinical validation and may harm the public health." The FDA invited LabCorp to discuss any validation strategies that might be underway in addition to the published studies. After meeting with LabCorp, FDA sent a

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[29] *Id.*

[30] *Response Genetics, Inc. Launches ResponseDX™ Tests to Select Institutions* (March 5, 2008), http://investor.responsegenetics.com/phoenix.zhtml?c=207260&p=irol-newsArticle&ID=1115473&highlight.

[31] *Id.*

[32] *FDA Draft Guidance: In Vitro Diagnostic Multivariate Index Assays*, at 3 (July 26, 2007), *available at* http://www.fda.gov/cdrh/oivd/guidance/1610.pdf.

[33] FDA Office of In Vitro Diagnostic Device Evaluation and Safety ("OIVD") Ovasure™ Manufacturer Letter (August 7, 2008), *available at* http://www.fda.gov/cdrh/oivd/labcorp_ltr.html.

Warning Letter to the company stating that the Ovasure™ test was a device that required either premarket approval or clearance.[34]

In another example, on March 10, 2005, FDA published a Final Rule classifying the Roche Amplichip CYP450 Test (2D6) into Class II, giving it the generic name "drug metabolizing enzyme (DME) genotyping system," and defining it as a device intended for use in testing deoxyribonucleic acid ("DNA") extracted from clinical samples to identify the presence or absence of human genotypic markers encoding a drug metabolizing enzyme. The device is used as an aid in determining treatment choices and individualizing treatment dose for therapeutics that are metabolized primarily by the specific enzyme for which the system provides genotypic information. The FDA identified the risks to health from the device as failure to correctly identify the DME genotype, which could lead to incorrect prediction of phenotype and result in incorrect patient management decisions.[35]

On March 10, 2005, FDA also published a Final Rule classifying the Affymetrix GENECHIP Microarray Instrumentation System into Class II, giving it the generic name "instrumentation for clinical multiplex test systems." It was defined as a device intended to measure and sort multiple signals generated by an assay from a clinical sample.[36] The FDA identified the risk to health from the device as potentially inaccurate results or inaccurate reports that may lead to incorrect diagnoses or patient evaluation, and FDA also found that a delay in diagnosis or a need for patient specimen re-collection can be a risk to health as well.[37]

On August 22, 2005, FDA cleared the Invader UGT1A1 Molecular Assay manufactured by Third Wave Technologies, Inc.[38] The UGT1A1 Molecular Assay detects variations in the UGT1A1 gene that produces UDP-glucuronosyltransferase, an enzyme that affects how certain drugs are broken down and cleared by the body. This information is useful to physicians to help determine the right drug dosage for individual patients and minimize harmful drug reactions, though other information may also affect dosing, such as the patient's liver function, age, kidney function, and co-administered drugs. At the time of approval, Lawrence Lesko, Ph.D., director of FDA's Office of Clinical Pharmacology and Biopharmaceutics in the Center for Drug Evaluation and Research stated in an FDA press release "Information on the UGT1A1 genotype can be an integral part of drug labels and will guide health professionals on

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[34] FDA Warning Letter to LabCorp (September 29, 2008), *available at* http://www.fda.gov/foi/warning_letters/s6947c.htm.

[35] *Medical Devices; Clinical Chemistry and Clinical Toxicology Devices; Drug Metabolizing Enzyme Genotyoing System*, 70 Fed. Reg. 11865 (March 10, 2005) (codified at 21 CFR § 862.3360).

[36] *Medical Devices; Clinical Chemistry and Clinical Toxicology Devices; Instrumentation for Clinical Multiplex Test Systems*, 70 Fed. Reg.11867 (March 10, 2005) (codified at 21 CFR § 862.2570).

[37] *Medical Devices; Immunology and Microbiology Devices; Classification of Ribonucleic Acid Preanalytical Systems*, 70 Fed. Reg. 49862 (August 25, 2005).

[38] *See 510(k) Substantial Equivalence Determination Decision Summary*, http://www.fda.gov/cdrh/reviews/K051824.pdf (last visited May 1, 2008).

how to dose medications such as irinotecan."[39] Irinotecan is a widely-used cancer therapeutic for colorectal cancer, and variations in the UGT1A1 gene can influence a patient's ability to break down irinotecan, which can lead to increased blood levels of the drug and potentially higher risks from the drug. [40]

We believe that an inconsistent application of regulatory oversight of LDTs poses a significant risk to patients. As discussed above with respect to Genentech's Herceptin therapy, there are tests on the market for the same therapeutic decision making purposes, some with FDA premarket review and some without. Given the potential risks associated with use of diagnostic tests that are sold with unsubstantiated or inadequately supported claims intended to guide specific drug or biologic therapeutic decision making, it is imperative that FDA expand its regulatory reach over such tests to ensure that any such claims made are scientifically and clinically proven. Regulation should be based on the type of diagnostic test produced and the associated claims made, not based on the type of entity producing the test.

LDT test results are being used by insurance companies and payers as a basis for denying coverage and reimbursement of certain therapies. For example, one insurance company will only agree to reimburse a patient for Genomic Health's OncotypeDx® breast cancer recurrence test if the patient agrees to forego adjuvant chemotherapy if the test score is low.[41] Genomic Health has not received FDA approval for the OncotypeDx® test, despite the claims made regarding the test's analytical and clinical utility. This example illustrates the willingness of payers to rely on claims made by clinical laboratories about their LDTs, further emphasizing the importance that such tests and associated claims undergo FDA review and approval prior to marketing.

C. Disparate Development and Review Pathways are not Justifiable

Some diagnostic tests are performed using diagnostic test kits that have received FDA approval or clearance. The companies that manufacture and market such diagnostic test kits

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[39] *FDA Clears Genetic Test That Advances Personalized Medicine - Test Helps Determine Safety of Drug Therapy* (August 22, 2005), *available at* http://www.fda.gov/bbs/topics/NEWS/2005/NEW01220.html.

[40] *Id.*

[41] In an Aetna Clinical Policy Bulletin Number 0352 dated December 1, 2006, Aetna sets forth five criteria to be met before Aetna will reimburse for the OncotypeDx® breast cancer recurrence test. Criteria no. 5 states: "Member and physician (prior to testing) have discussed the potential results of the test and agree to use the results to guide therapy (*i.e.*, member will forgo adjuvant chemotherapy if OncotypeDx score is low." http://www.aetna.com/cpb/medical/data/300_399/0352.html (last visited November 17, 2008). A different conclusion was reached by UnitedHealthCare, which states in its policy on testing for breast cancer recurrence, "[a] physician cannot with assurance withhold chemotherapy based upon the prediction of low risk of recurrence from gene expression profiling assays." https://www.unitedhealthcareonline.com/b2c/cmaIndexResult.do?channelId=016228193392b010VgnVCM100000c520720a____&htmlFilePath=/ccmcontent/ProviderII/UHC/en-US/Assets/ProviderStaticFiles/ProviderStaticFilesHtml/MedicalPolicies/Genetic_Testing_of_Tumor_Tissue_to_Predict_Breast_Cancer_Recurrence.htm (last visited November 16, 2008).

have had to do significant development work, prepare an application for review by FDA, and wait for that review to be completed before their diagnostic test kits can be sold. Conversely, other diagnostic tests can be sold by a clinical laboratory with much less development work, limited or no clinical validation, no application, no review period, and no FDA oversight – either pre-market or post-market. As a result, two essentially identical *in vitro* diagnostic tests used for the exact same intended use – to guide drug or biologic therapy – have highly disparate development and premarket submission and post-market compliance requirements. Indeed, the different regulatory treatment of diagnostic test kits and LDTs likely accounts for the decrease in the number of kits being brought to FDA for review in the last five years, and concomitant increase in LDTs that are less-regulated.

The FDA has not provided a rationale as to why one of those tests is regulated and the other is not. Nor, we submit, are there appropriate policies or scientific reasons that might justify the disparate treatment, especially in light of the increasing number of high risk diagnostics intended to guide treatment decisions for critical life-extending therapeutics. After all, the *in vitro* tests are used for the same purpose, and the risks to patients for deficiencies in the tests do not vary based on whether the test is performed using a diagnostic test kit or an LDT. Thus, under the District of Columbia District Court's holding in *Bracco Diagnostics v. Shalala*, 963 F. Supp. 20, 27-28 (D.D.C. 1997), FDA's failure to regulate all diagnostic tests with the same standards could be seen as arbitrary and capricious. To overcome this problem, FDA should (1) hold all diagnostic tests to the same standards; (2) bring enforcement cases against clinical laboratories and associated companies that make or market LDTs with unsubstantiated claims intended to guide specific drug or biologic therapeutic decision making; and (3) initiate rulemaking to make consistent and transparent the review system and standards for all diagnostic tests. The FDA's legal authority to regulate LDTs is well established, and is described in greater detail below.

IV. FDA HAS THE LEGAL AUTHORITY TO REGULATE LDTS

As noted in our March 2, 2007 comments to the IVDMIA draft guidance docket, Genentech agrees with FDA that it has the authority to regulate all LDTs, even though the Agency has chosen not to regulate them in the past.[42] The FDA briefly laid out its rationale for its regulatory authority over all LDTs in its first and second versions of its draft IVDMIA guidance document.[43] In both versions, the Agency stated that LDTs, in particular the subset

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[42] *See* Genentech's comments to IVDMIA draft guidance (March 2, 2007), *available at* http://www.fda.gov/ohrms/dockets/dockets/06d0347/06D-0347-EC83-Attach-1.pdf.

[43] The FDA changed its characterization of the LDTs it wants to regulate from the first to the second draft guidances; however, the agency's legal position has not changed. We also note that FDA could regulate pharmacogenomic LDTs as biologics just as the agency has regulated blood and HIV LDTs as biologics under FDCA and the Public Health Service Act. For example, FDA reviews and approves all assay test kits used to detect infectious and transmissible diseases in donated blood. *See Keeping Blood Transfusions Safe: FDA's Multi-layered Protections for Donated Blood*, Pub. No. FS02-1 (February 2002), *available at* http://www.fda.gov/opacom/factsheets/justthefacts/15blood.pdf. Companies may not use unapproved LDTs to test blood. Similarly, FDA has periodically taken enforcement action against companies that provided HIV testing through means other than FDA-approved test kits. *See, e.g., Letters Sent to Test Labs, HIV Kit Manufacturers,*

of LDTs that were multivariate index assays, were medical devices because "'clinical laboratories that develop (in house) tests are acting as manufacturers of medical devices and are subject to FDA jurisdiction under the Act.'"[44]

In the docket created for the IVDMIA draft guidance documents, several commenters suggested that FDA lacked legal authority to regulate LDTs; we respectfully disagree. Rather, as outlined below, Genentech believes FDA has ample legal authority to regulate LDTs, and that FDA's decision to limit application of the draft guidance to IVDMIAs is not sufficiently responsive to public health concerns raised by the growing availability of LDTs.

A. FDA Recognized that LDTs Could Be Regulated as Medical Devices as a Result of the 1976 Medical Device Amendments

The regulation of LDTs is tied to the regulation of all medical devices, and in particular other diagnostic tests and test systems, including genetic tests and tests that measure proteins and protein markers (*e.g.*, enzymes) that result from genes. Before 1938, FDA did not regulate medical devices. In 1938, through major revisions to the 1906 Pure Food and Drugs Act,[45] which resulted in FDCA,[46] FDA was given limited authority over medical devices.[47] At that time, there was no regulatory mechanism for the premarketing approval of devices, though "misbranded" and "adulterated" devices could not be shipped in interstate commerce. There was, however, a more extensive regulatory system for "drugs," and FDA tried, on a case-by-case basis, to expand the definition of drugs to include some medical devices.[48]

The 1976 Medical Device Amendments to the FDCA[49] (the "1976 Amendments") dispelled any doubt over FDA's authority over clinical laboratory testing and the use of *in vitro* diagnostics. The 1976 Amendments provide explicit authority over the regulation of *in vitro*

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and Trade Associations (September 26, 1991), *available at* http://www.fda.gov/bbs/topics/ANSWERS/ANS00339.html. The legal rationale for why the Center for Biologics Evaluation and Review can enforce requirements for IVDs for blood and other samples tested for donor suitability or HIV against parties including clinical laboratories are identical to the legal rationale we are espousing, that is, that the tests are medical devices.

[44] Draft Guidance - IVDMIAs, at 3 (July 26, 2007), *available at* http://www.fda.gov/cdrh/oivd/guidance/1610.pdf, *quoting Medical Devices; Classification/Reclassification; Restricted Devices: Analyte Specific Reagents*, 62 Fed. Reg. 62243, 62249 (November 21, 1997).

[45] 34 Stat. 768 (1906).

[46] 52 Stat. 1040 (1938).

[47] Prior to 1976. devices were then defined as "instruments, apparatus and contrivances, including their components, parts and accessories, intended (1) for use in diagnosis, cure, mitigation, treatment, or prevention of diseases in man or other animals; or (2) to affect the structure or any function of the body of man or other animals." *See* 21 U.S.C. 321(h) (1964 ed.)

[48] For example, in the 1970s, there were screening programs for sickle cell disease, Tay-Sachs disease, neural tube defects, and Down Syndrome, and FDA attempted, with some success, to regulate some of these *in vitro* diagnostic tests through the "drug" provisions of the law.

[49] Pub. L. 94-295, 90 Stat. 539 (1976).

reagents and other items used to create an LDT. Specifically, the medical device definition was expanded to include "an instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article, including any component, part, or accessory," which is recognized in various authoritative texts[50] "intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals," or which is "intended to affect the structure or any function of the body of man" and which is not a drug.[51] The FDA also made certain that any *in vitro* diagnostic testing could be regulated as a medical device through its implementing regulations. The FDA defined "*in vitro* diagnostic" ("IVD") by regulation (21 CFR § 809.3(a)) as follows:

> *In vitro diagnostic products* are those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. These products are devices as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (the act) and may also be biological products subject to section 351 of the Public Health Service Act.

The FDA's regulatory definition, which includes the "examination of specimens" and the "systems" used in disease diagnosis, provides a solid basis for FDA regulation of *in vitro* testing performed by clinical laboratories, including pharmacogenomic tests and other LDTs directly tied to drug or biologic use.[52] When a clinical laboratory develops and performs an LDT, it is using a variety of reagents, instruments, and other medical devices in a systematic way to examine a specimen from the human body. Almost every product used by the laboratory is a medical device, and the aggregated system of testing is a separate medical device. For this reason, there is no statutory or regulatory distinction that can reasonably be drawn between an LDT that the clinical laboratory develops itself and an aggregated test system or kit that is manufactured by another entity and sold to the clinical laboratory, especially when the LDT and the system or diagnostic test kit are intended to be used for the same or closely related purpose.

The FDA's belief in its regulatory jurisdiction over LDTs is also evident from its early rulemaking to classify all of the medical devices that were on the market when the Medical Device Amendments were enacted. Specifically, FDA defined and began to regulate all hematology and pathology devices used in clinical laboratories, including dye and chemical solution stains, cell and tissue culture supplies and equipment, chromosome culture kits, tissue processing equipment, specimen transport and storage containers, and general purpose

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[50] The "authoritative texts" referred to in the law, FDCA § 201(h), were the official National Formulary and the United States Pharmacopeia. The National Formulary is no longer published.

[51] FDCA § 201(h).

[52] IVD's – both the laboratory test systems that are sold by a manufacturer as a kit or developed by a clinical laboratory as an LDT – are regulated by FDA's OIVD of the Center for Devices and Radiological Health ("CDRH"). However, since the specimens tested are biological products, the tests could also be regulated by FDA's Center for Biologics Research and Evaluation ("CBER") under the Public Health Service Act and FDCA.

reagents, among many others.[53] The definition of a "general purpose reagent" again demonstrates that FDA recognized that clinical laboratories, by using a variety of reagents and other equipment, were creating a finished medical device – an *in vitro* diagnostic test product, comprised of reagents, instruments, and systems. "General purpose reagent" is defined at 21 CFR § 864.4010(a) in relevant part as follows:

> A general purpose reagent is a chemical reagent that has general laboratory application, that is used to collect, prepare and examine specimens from the human body for diagnostic purposes, and that is not labeled or otherwise intended for a specific diagnostic application. It may be either an individual substance, or multiple substances reformulated, which, when combined with or used in conjunction with an appropriate analyte specific reagent (ASR) and other general purpose reagents, is part of a diagnostic test procedure or system constituting a finished in vitro diagnostic (IVD) test.

Thus, since FDA rulemaking in 1980, every *in vitro* diagnostic test performed in a clinical laboratory, including LDTs, meets FDA's definition of a "finished *in vitro* diagnostic test" product, over which FDA can assert its entire medical device regulatory authority. Depending on the classification of the LDT,[54] FDA could prohibit the sale of an LDT until it had undergone review by FDA. Initially, FDA placed most IVDs into Class I (general controls), and devices in Class I had to provide to FDA notifications under section 510(k) before marketing.[55] Later, in 1989, FDA issued regulations exempting from 510(k) premarket notification many low risk devices, including various IVD test products, "to reduce the number of unnecessary premarket notifications, thereby freeing agency resources for the review of more complex notifications."[56]

The FDA limited these exemptions from 510(k) notifications in several important ways: a 510(k) notification is still required if:

1) the device is intended for a use different from the intended use of a related legally marketed device;
2) the device uses "a different fundamental scientific technology" than a related legally marketed device; or

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[53] 21 CFR §§ 864.1850, 864.2240, 864.2260, 864.3010, 864.3250, 864.4010.

[54] Under the 1976 Amendments, all devices on the market at the time the amendments were enacted had to be "classified" into one of three levels of regulatory control based on risk in order to provide reasonable assurance of the devices' safety and effectiveness: Class I (general controls), Class II (performance standards), or Class IIII (premarket approval). For an IVD, the classification depends on the "intended use," (i.e., what is being tested), and the "indication for use," (i.e., why the patient would be tested). Classification of devices generally is based on the potential risk to the patient or user, whereas in the case of an IVD, the risk to health is based on the value of a correct decision and the harm or risk of a false negative or false positive result.

[55] The 1976 Amendments also established two different pathways by which a manufacturer could obtain FDA review of its device before marketing. The most commonly used approach is the premarketing "clearance" process under section 510(k) of FDCA. [55] The less common, generally more data-intensive scheme is the "premarket approval application" ("PMA") process through which the manufacturer must provide data and information showing that its device is safe and effective for use, and, based on that data, FDA determines whether or not to approve the device for marketing.

[56] *Medical Devices; Exemptions from Premarket Notifications for Certain Classified Devices,* 54 Fed. Reg. 25042 (June 12, 1989).

3) the device is an *in vitro* device that is intended
   a) for use in the diagnosis, monitoring, or screening of neoplastic diseases;
   b) for use is used in screening or diagnosis of familial or acquired genetic disorders;
   c) is used to measure a surrogate marker for screening, diagnosis, or monitoring life-threatening diseases or to monitor therapy;
   d) is used to assess the risk of cardiovascular disease or to manage diabetes;
   e) is used to identify microorganisms from clinical material;
   f) for detection of certain antibodies;
   g) for noninvasive testing (as defined at 21 CFR § 812.3(k)); or
   h) for point of care patient testing.[57]

Since virtually all pharmacogenomic and other LDTs now used to determine drug and biologic therapy either employ a "different fundamental scientific technology" than existed when IVDs were first classified, or are used for one of the non-exempt purposes specified above, or have not been classified, the exemption from premarket review should not generally apply to LDTs. Indeed, in its Guidance on Pharmacogenetic Tests and Genetic Tests for Heritable Markers, FDA made clear that, "[w]e expect that most pharmacogenetic and genetic device submissions will be traditional 510(k)s or de novo classifications.[58] However, some devices will require submission of a PMA (see sections 513 and 515 of the Federal Food, Drug, and Cosmetic Act (Act) (21 U.S.C. 360c, 360e))."[59] The same guidance further notes that, for PMA and de novo submissions (*i.e.*, submissions for high-risk and novel tests), clinical data should be provided to substantiate the test's effectiveness.

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[57] 21 CFR § 864.9; Examples of different uses are described as follows: "*e.g.*, the device is intended for a different medical purpose, or the device is intended for lay use where the former intended use was by health care professionals only." 21 CFR § 864.9(a). We recognize that a court might be reluctant to impose stricter regulatory controls on devices, such as general purpose reagents, used for a wide variety of purposes. *United States v. Undetermined Number of Unlabeled Cases,* 21 F.3rd 1026, 1029 (10th Cir. 1994) (specimen cups used to collect saliva and urine for HIV testing were not Class III devices because containers were not new and were not used in a new manner). However, here, an *in vitro* diagnostic test product is a new product created by combining a variety of reagents, instruments, and systems and is intended for medical diagnostic use.

An example of a different fundamental scientific technology was described as "*e.g.*, ...an *in vitro* diagnostic device detects or identifies infectious agents by using a deoxyribonucleic acid (DNA) probe or nucleic acid hybridization technology rather than culture or immunoassay technology." 21 CFR § 864.9(b). This example reinforces our position that FDA should assert more regulatory jurisdiction over LDTs when used to determine appropriate drug or biologic use, since the general reagents and other devices, when used for drug or biologic-specific testing, which is almost always genetic testing, fall within these limitations and, thus, would require 510(k)s for that use.

[58] Under the de novo classification process, FDA may statutorily reclassify certain low-risk devices that have been automatically classified into Class III by operation of FDCA following the submission of a 510(k) and a finding that the device is not substantially equivalent (NSE) to any identifiable predicate device. If successfully reclassified, the device may be legally marketed and used as a predicate for future 510(k) submissions for similar devices. *See* FDCA § 513(f)(2) and *New Section 513(f)(2) - Evaluation of Automatic Class III Designation, Guidance for Industry and CDRH Staff* (February 19, 1998), *available at* http://www.fda.gov/cdrh/modact/classiii.html.

[59] *FDA Guidance – Pharmacogenetic Tests and Genetic Tests for Heritable Markers* at 2 (June 19, 2007), *available at* http://www.fda.gov/cdrh/oivd/guidance/1549.pdf.

As is evident, FDA conclusively determined 28 years ago that all LDTs are, in regulatory parlance, *in vitro* diagnostic test products subject to regulation. The 1976 Amendments and the 1980 rulemaking alone provide ample authority for FDA to assert additional regulatory jurisdiction over all LDTs, including all LDTs used in therapeutic decision making. In addition, for the reasons mentioned above, most, if not all, LDTs used in therapeutic decision making should require either a 510(k), PMA, or de novo submission.

B. FDA Proposed Regulation of Some Clinical Laboratory Activities in 1980

Notwithstanding this clear statutory grant of authority, some commenters have suggested that FDA cannot regulate the activities or "services" taking place within a clinical laboratory. History refutes that argument. The FDA has long taken the position that it can regulate clinical laboratory activities when necessary to assure the safe and effective use of medical devices, including *in vitro* diagnostic tests. In 1980, FDA published a proposed rule that would have established restrictions on the sale, distribution, and use of alpha-fetoprotein ("AFP") test kits sold by manufacturers to clinical laboratories for detection of neural tube defects.[60] The AFP proposed rule demonstrates that FDA acknowledged the risks of associated with was willing to regulate activities that take place within a clinical laboratory and acknowledged. Although in 1983 FDA decided not to regulate AFPs,[61] the Agency did not retreat from its position that it had jurisdiction to do so.

C. FDA Recognized Its Authority Over LDTs in the Context of Early Genetic Testing

The early 1990s saw an increasing number of genetic tests being offered, including two that raised significant controversy, the Breast Cancer Gene 1 ("BRACA 1") and Breast Cancer Gene 2 ("BRACA 2") tests offered by clinical laboratories to determine which women may be genetically predisposed to developing breast cancer. In 1994, FDA held internal meetings, and later met with the National Institutes of Health ("NIH") and the Department of Health and Human Services ("DHHS"), to discuss whether there was a need for regulation of LDTs used in genetic testing. In 1995, clinical laboratories began to offer commercial multiplex genetic screening assays without seeking FDA clearance. As the number of such tests increased, FDA again considered whether to regulate LDTs used for genetic testing. Entities both inside and outside the federal government urged FDA to provide a legal and regulatory framework for oversight of the growing genetic testing industry.[62]

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[60] *Alpha-Fetoprotein Kits*, 45 Fed. Reg. 74158 (November 7, 1980) (Proposed Rule). This is a classic case of how different intended uses can drive different levels of regulation. FDA proposed to impose regulatory requirements on clinical laboratory personnel, procedures, reporting, etc. for AFP tests used to determine neural tube defects in fetuses, but not the same test used for cancer diagnoses.

[61] *Alpha-Fetoprotein Kits; Withdrawal of Proposed Rule*, 48 Fed. Reg. 27780 (June 17, 1983).

[62] *See, e.g.*, MJ Malinowski and MA O'Rourke, *A False Start? The Impact of Federal Policy on the Genotechnology Industry*, 13 Yale J. on Reg. 163 (1996); MJ Malinowski and RJR Blatt, *Commercialization of Genetic Testing Services: The FDA, Market Forces, and Biological Tarot Cards*, 71 Tul. L. Rev. 1211 (1977).

The FDA sought guidance on what role it should play, and on January 22, 1996, held a meeting of its Immunology Devices Panel, and asked the Panel, among other questions, to consider the regulatory controls that should be put into place for commercially marketed ASRs.[63] At this meeting, Dr. Steven Gutman, then Director of the Division of Clinical Laboratory Devices, explained FDA's regulatory authority over all LDTs:

> There is a final 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.
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> * * *
>
> 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....[64]

While FDA expressed its concerns about the in-house tests conducted within clinical laboratories, the Agency did not attempt to regulate the tests developed by clinical laboratories,[65] proposing instead to regulate all ASRs—the tests' active ingredients. ASRs that were used to diagnose potentially fatal contagious conditions (*e.g.*, HIV or tuberculosis) or used to safeguard the blood supply were to be treated as Class III medical devices subject to premarket approval, while the remainder of ASRs, including those used in genetic tests, were to be regulated through Class I general controls.[66]

Although FDA decided not to use its discretion to regulate the in-house clinical tests (LDTs) at that time, it clearly cautioned that additional controls might be warranted:

> However, at a future date, the agency may reevaluate whether additional controls over the in-house tests developed by such laboratories may be needed to provide an appropriate level of consumer protection. Such controls may be especially relevant as

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[63] *Advisory Committee; Notice of Meeting*, 61 Fed. Reg. 74-75 (January 2, 1996). ASRs are "reagents composed of chemicals or antibodies that may be thought of as the "active ingredients" of diagnostic tests that are used to identify one specific disease or condition." *Medical Devices; Classification/Reclassification; Restricted Devices; Analyte Specific Reagents,* 62 Fed, Reg, 62243, 62244 (November 21, 1997) ("ASR Final Rule"). Examples of ASRs include monoclonal and polyclonal antibodies, deoxyribonucleic acid (DNA) probes, nucleic acid sequences, viral antigens, and ligands. 21 CFR § 809.10(e)(1); 21 CFR § 864.4020(a).

[64] Transcript of the Immunology Devices Panel of the Medical Devices Advisory Committee meeting, at 21, 23 (January 22, 1996).

[65] *Medical Devices; Classification/Reclassification; Restricted Devices; Analyte Specific Reagents*, 61 Fed. Reg. 10484 (March 14, 1996) ("ASR Proposed Rule").

[66] ASR Proposed Rule, 61 Fed. Reg. at 10486. The FDA also used the "restricted device" authority of FDCA 505(e), and proposed that ASRs used to produce in-house clinical laboratory developed tests be restricted to those clinical laboratories certified under CLIA-88 as "high-complexity laboratories." FDA determined that those laboratories "have the expertise and qualifications required to use these active ingredients in making in-house tests, and to assure the performance of the ASRs." The FDA made clear that it is "the laboratory producing the test, not the manufacturer of the ingredients [that] is accountable for use of the ingredient and its performance as part of the test." *Id.*

> testing for the presence of genes associated with cancer or dementing diseases become more widely available. Additional controls might include a broad array of approaches, ranging from full premarket review by FDA to use of third parties to evaluate analytical or clinical performance of the tests. The laboratories producing tests from ASR's and offering the tests as laboratory services are currently regulated by the Health Care Financing Administration (HCFA) [now CMS] under the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88) for compliance with general laboratory standards regarding personnel, proficiency testing, quality control, and quality assurance. However, these HCFA regulations do not include the same product controls provided by FDA. As a result, neither patients nor practitioners have assurance that all ingredients in the laboratory developed tests are of high quality and capable of producing consistent results.[67]

Again, ASR rulemaking illustrates that FDA was confident that it had the authority to take additional steps to regulate LDTs developed in-house by clinical laboratories. It also understood that CLIA might not provide adequate assurance of quality and reliability, and that FDA and the Centers for Medicare & Medicaid Services ("CMS," then the Health Care Financing Administration or "HCFA"), had the authority to regulate clinical laboratories co-extensively.

The Agency took the same position in the preamble to the 1997 ASR Final Rule, asserting 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."[68] The FDA's Immunology Panel suggested that the active ingredients in human genetic tests be more stringently regulated and that genetic tests should be required to obtain premarketing clearance or approval.[69] The FDA asked for comments on the "full range of options" available to regulate ASRs used for human genetic testing.[70] It also noted that it could limit the labeling and promotional materials used by clinical laboratories.[71]

The FDA, however, did not exercise its regulatory authority over all ASRs as proposed. Rather, FDA took steps to control the use of ASRs. In particular, FDA limited the sales and marketing of ASRs by:

1) Requiring ASR labels to state that the analytical and performance characteristics of the ASR had not been established;
2) Restricting sales of ASRs to specific groups;[72]

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[67] *Id.*

[68] ASR Final Rule, 62 Fed. Reg. at 62249.

[69] ASR Proposed Rule, 61 Fed. Reg. at 10486.

[70] *Id.*

[71] *Id.* at 10487.

[72] FDA restricted sales to *in vitro* diagnostic manufacturers, clinical laboratories qualified to perform high complexity testing under CLIA, and organizations that use the reagents to make tests for purposes other than providing diagnostic information to patients and practitioners, *e.g.*, forensic, academic, research and other nonclinical laboratories. 21 CFR § 809.30(b).

3) Requiring clinical laboratories developing LDTs using ASRs to explain to customers that the laboratory had developed and ascertained the performance characteristics of the test and that the test had not been cleared or approved by FDA; and
4) Limiting the ordering of tests developed using ASRs to physicians and other licensed health care practitioners.[73]

Three of these controls are regulatory requirements imposed on the clinical laboratories, not on ASR manufacturers, illustrating how FDA has already begun to exercise substantial regulatory jurisdiction over clinical laboratories. The FDA treats the clinical laboratories as manufacturers of a medical device – the test assay and result – which are, in regulatory terms, an *in vitro* diagnostic test product. Under this approach, FDA controls the "labeling" of the "device" sold by the clinical laboratory and the "sales" of the medical device to licensed professionals.

At the conclusion of the ASR rulemaking process, three different sets of regulatory controls were implemented. The controls applied to the tests performed in clinical laboratories depended on whether the tests was performed using (1) a diagnostic test kit sold by an *in vitro* diagnostic manufacturer, (2) one or more ASRs (an LDT or so-called "home brew" test), or (3) one or more general purpose reagents and/or laboratory-developed ASRs (an LDT or so-called "home brew-home brew" test). The FDA imposed the highest regulatory burden on the diagnostic test kit manufacturers, and, consequently *in vitro* diagnostic tests in kit form had the highest probability of being analytically and clinically valid. An intermediate burden was placed on clinical laboratory LDTs comprising ASRs. Specifically, the "active ingredients" of the tests – ASRs – were required to be properly manufactured and labeled, the clinical laboratories had to be qualified to perform "high complexity" testing, and health care providers ordering these tests had to be informed by the clinical laboratory in the test report that "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."[74] Perhaps because FDA could not anticipate fully their existence and impact on treatment decisions, FDA imposed the least stringent controls over the LDTs that are most likely to have analytical and clinical validity problems – the LDTs comprising general purpose reagents and/or laboratory-developed ASRs.[75] For those "home brew-home brew" tests, FDA imposed essentially no

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[73] 21 CFR § 809.30. Although FDA decided not to regulate all ASRs as proposed, it stated that it might consider additional regulation of genetic testing in the future.

> FDA is aware of the public concern and desire that the regulation of products used in genetic testing be done in a thoughtful and product manner. As stated previously, FDA intends, with this regulation, to establish appropriate initial controls for ASR's use in genetic tests and to review agency policies relating to many aspects of regulation of recommendations from the National Institute of Health's (NIH's) Task Force on Genetics Testing and other interested parties. After this review, FDA may propose additional regulation of genetic tests.

ASR Final Rule, 62 Fed. Reg. at 62246.

[74] 21 CFR § 809.30(e).

[75] The majority of laboratories conduct genetic testing using LDTs that do not use commercially-distributed ASRs. "According to a survey of 190 genetic- testing laboratory directors conducted by the Genetics and Public Policy

controls. Even if this approach may have been sufficient in the past, it is no longer, because the increasing number of LDTs and the use of the results to inform patient treatment options without sufficient analytical and clinical validation.

D. FDA Again Acknowledges Its Regulatory Authority Before the Secretarial Advisory Committee on Genetic Testing (SACGT) and the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS)

In response to the recommendations of the NIH Department of Energy Working Group on Ethical, Legal, and Social Implications of Human Genome Research's Task Force on Genetic Testing,[76] the DHHS Secretary created the Secretarial Advisory Committee on Genetic Testing ("SACGT"). From 1999 through 2002, SACGT considered the extent to which FDA and other DHHS agencies should exercise regulatory control over genetic testing. SACGT held several meetings and discussed to what extent, if at all, FDA should regulate genetic tests. During these meetings, FDA repeatedly advised SACGT that it had jurisdiction over LDTs.[77] Officials at FDA worked extensively with SACGT to create a proposed classification scheme for deciding which genetic LDTs would be regulated.[78] The FDA also publicly explained that it had jurisdiction over LDTs and the legal basis for its position.[79] The Agency further stated that it was going to initiate rulemaking to require premarket submissions of LDT ("home brew") applications to FDA, but that rulemaking would have to follow the efforts of SACGT to develop a classification scheme for genetic tests.[80]

Ultimately, SACGT could not create a satisfactory classification scheme, but recommended that FDA continue its efforts to develop an innovative regulatory process for genetic tests, whether LDTs or otherwise. SACGT was disbanded in 2002 without having reached a definitive conclusion about the regulatory course DHHS should follow; however, DHHS Secretary Tommy Thompson created another Secretarial advisory committee, called

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Center in 2006, 89 percent of laboratories offer at least some LDTs without ASRs, including 29 percent that exclusively use ASR-free LDTs and another 19 percent who use them for the majority of their tests. Just 5 percent said that they employ FDA approved ASRs in all of the tests they perform." GH Javitt, *In Search of a Coherent Framework: Options for FDA Oversight of Genetic Tests*, 62 Food & Drug L.J. 617 (2007).

[76] See Final Report of the Task Force on Genetic Testing: Promoting Safe and Effective Genetic Testing in the United States (September 1997), *available at* http://www.genome.gov/10001733.

[77] *See* SACGT meeting transcripts and reports, *available at* http://oba.od.nih.gov/SACGHS/sacgt_info.html (last visited November 18, 2008).

[78] *Secretary's Advisory Committee on Genetic Testing*, 65 Fed. Reg. 76643 (December 7, 2000) (request for public comment on a proposed classification methodology for determining level of review for genetic tests).

[79] For example, at the February 15, 2001 SACGT meeting, Dr. David Feigal, then Director of FDA's CDRH, Dr. David Feigal explained: "This will not be an unchallenged assertion, that FDA should start regulating home-brewed tests. There will be those who say this is the practice of clinical pathology medicine and is not something that FDA has jurisdiction over. From our perspective, it's the practice of clinical pathology with a medical device, and that moves it back into our jurisdiction." Transcript of SACGHT meeting at 51, (February 15, 2001) *available at* http://oba.od.nih.gov/oba/sacgt/transcripts/Feb15gttrans.pdf.

[80] *Id.* at 30-34.

the Secretary's Advisory Committee on Genetics, Health, and Society ("SACGHS").[81] Pharmacogenomic issues were the subject of extensive discussion at the October 2005, March 2006 and March 2007 SACGHS meetings.[82] At the March 2007 SACGHS meeting, FDA expressed confidence in its regulatory authority over LDTs, taking the position that it has the expertise to make risk-based decisions concerning LDTs.[83] In the April 2008 SACGHS Oversight Report, SACGHS, like its predecessor SACGT, proposed that FDA more extensively regulate genetic LDTs, stating that FDA should address all LDTs "regardless of how they are produced (*i.e.*, as a commercial test kit or laboratory-developed test), in a manner that takes advantage of its current expertise."[84])

E. FDA Denied a Citizen Petition that Asserted FDA Has No Jurisdiction Over LDTs

At least two groups have filed Citizen Petitions arguing that FDA should reverse its jurisdictional position and state that it will not regulate LDTs as medical devices. In 1992, Hyman, Phelps & McNamara, PC, filed a Citizen Petition requesting that the Commissioner not regulate as medical devices "assays developed by clinical reference laboratories strictly for in-house use."[85] The petitioner argued that FDA lacks authority to regulate clinical laboratories or the testing services offered by clinical laboratories, including LDTs. The FDA denied that Petition in 1998.[86] In 2006, the Washington Legal Foundation filed a Citizen Petition requesting that FDA not regulate LDTs as medical devices.[87] The FDA has not yet responded to that Citizen Petition.

F. CLIA is Not an Impediment to Regulation by FDA

Some argue that because CMS has jurisdiction over clinical laboratories pursuant to CLIA, clinical laboratories cannot and should not be regulated by FDA. CLIA does not preempt

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[81] *See* SACGHS activities, *available at* http://oba.od.nih.gov/SACGHS/sacghs_home.html (last visited November 18, 2008).

[82] *See* Transcript of October 2005 SACGHS meeting (October 19-20, 2005), *available at* http://oba.od.nih.gov/SACGHS/sacghs_past_meeting_documents.html#oct2005; Transcript of March 2006 SACGHS meeting (March 27-28, 2006), *available at* http://oba.od.nih.gov/SACGHS/sacghs_past_meeting_documents.html#mar2006; Transcript of March 2007 SACGHS meeting (march 26-27, 2007), *available at* http://oba.od.nih.gov/SACGHS/sacghs_past_meeting_documents.html#mar2007.

[83] *See* Transcript of March 2007 SACGHS meeting (March 26-27, 2007), *available at* http://oba.od.nih.gov/SACGHS/sacghs_past_meeting_documents.html#mar2007.

[84] SACGHS Letter to DHHS Secretary Michael O. Levitt (April 30, 2008), *available at* http://oba.od.nih.gov/oba/SACGHS/reports/GenTest_letter_to_Sec_042707.pdf; *SACGHS Report, U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services,* at 191(April 2008), *available at* http://oba.od.nih.gov/oba/SACGHS/reports/SACGHS_oversight_report.pdf.

[85] *See* FDA Docket No. 1992P-0405.

[86] *Id.*

[87] FDA Docket No. 2006P-0402, *available at* http://www.fda.gov/ohrms/dockets/dockets/06p0402/06p0402.htm (last visited November 18, 2008).

FDA's authority under FDCA, including its authority to regulate clinical laboratory protocols. As one District Court explained:

> The provisions of the FDCA and CLIA are not inconsistent. The "diagnosis, prevention, or treatment" language in section 263a parallels the "diagnosis ... or treatment, or ... prevention" language in the FDCA. *Compare* 42 U.S.C.S. § 263a(a) *with* 21 U.S.C.S. § 321(h)(2). In addition, CLIA regulations require laboratories subject to HCFA jurisdiction to comply with "all applicable Federal ... laws." 42 C.F.R. § 493.701 (1991). It appears, therefore, that Congress intended to leave some regulatory overlap between FDCA and CLIA.[88]

While CMS has regulatory jurisdiction under CLIA, FDA has concurrent jurisdiction under FDCA.[89] It is common for two federal agencies to have concurrent jurisdiction.[90] The Secretary of DHHS simply delegated the financial management and administrative operations of CLIA to CMS.[91] Effective October 31, 2003, the Secretary of DHHS delegated to FDA primary responsibility for the categorization of commercially marketed *in vitro* diagnostic tests under CLIA based on their potential risk to public health.[92] Any potential inconsistency between FDCA and CLIA laboratory requirements, obsolete or duplicative requirements, or new requirements needed to address changes in technology, can be handled through enforcement discretion or rulemaking, as they have in the past.

V. FDA HAS THE SKILLS, SYSTEMS, REGULATORY FLEXIBILITY, AND RESOURCES TO REGULATE ALL LDTs

The FDA has the scientific skills and mechanisms required for the regulatory oversight of all diagnostic tests used in therapeutic decision making and can take advantage of its current experience in mandatory registration, evaluating laboratory tests, compliance, quality assurance and post marketing surveillance and reporting. In addition, FDA has wide latitude under FDCA with respect to the type, intensity, and timing of regulatory requirements. The FDA is thus well-suited to review all tests used in therapeutic decision making – whether LDTs or kits – while furthering innovation in diagnostic development.

Registration and Other Information: The FDA has the legal authority to require that all medical device manufacturers register with FDA and provide the Agency with a list of the

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[88] *Clinical Reference Laboratory, Inc., v. Sullivan*, 791 F. Supp. 1499, 1509 (D. Kan. 1992), *aff'd in part, rev'd in part on other grounds, United States v. Undetermined Number of Unlabeled Cases*, 21 F.3rd 1026 (10th Cir. 1994).

[89] *Medicare, Medicaid and CLIA Programs; Revision of the Clinical Laboratory Regulations for the Medicare, Medicaid, and Clinical Laboratories Improvement Act of 1967 Programs*, 53 Fed. Reg. 29590, 29590-91 (Aug. 5, 1988) ("CLIA Proposed Rule").

[90] For example, FDA and the Department of Agriculture both have authority over certain foods; the FDA and the Federal Trade Commission both have authority over certain advertisements; and FDA and the Environmental Protection Agency share authority over certain pesticides.

[91] *See* http://www.fda.gov/CDRH/CLIA/index.html (last visited November 18, 2008).

[92] *FDA Delegation of Authority,* 68 Fed. Reg. 64350 (November 13, 2003).

medical devices (specifically, LDTs) that they are manufacturing.[93] We agree with the recommendation of SACGHS that such a mandatory registry of LDTs be made public.[94] If FDA requires LDTs to register and list their LDTs under FDCA, that information should be publicly available on FDA's web site.[95] In addition, under the Food and Drug Administration Amendments Act of 2007 ("FDAAA"), FDA was also give the authority to require companies to include information about medical device trials in the clinical trial registry and results database expanded by that law.[96] Through this mechanism, information would be available to the medical community and the public about the clinical validity of LDTs.

Review: The FDA has conducted scientific and medical review of diagnostic tests for years when those tests have been submitted to the Agency for review as medical device kits. The FDA has also written numerous documents providing information to pharmacogenomic test developers about the scientific standards that would apply to their tests.[97] Thus, FDA is well equipped to handle this task.[98] In addition, to avoid any impact on innovation, FDA might decide to use third parties to review 510(k) premarket notifications.[99]

Compliance: One question that inevitably arises is whether a device manufacturer is complying with the applicable law; for example, whether it is keeping the necessary records or filing the required reports. The FDA has broad inspectional authority over medical device manufacturers, and could inspect clinical laboratories for compliance.[100] The FDA can also use accredited persons to conduct inspections,[101] and might be able to use CLIA personnel or professionals from accrediting organizations to augment its inspections through this mechanism.

Quality Assurance: Testing of human biological specimens requires properly trained personnel, suitable reagents and other materials, properly calibrated equipment, adherence to sound protocols and other similar requirements. The FDA has promulgated quality systems regulations that could be used by clinical laboratories to make certain that their testing is of the

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[93] *See* FDCA § 510.

[94] SACGHS Report, *U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services* at 8 (April 2008), *available at* http://oba.od.nih.gov/oba/SACGHS/reports/SACGHS_oversight_report.pdf.

[95] *See* CDRH web link to registration and listing information, *available at* http://www.fda.gov/cdrh/registration/search.html (last visited July 23, 2008).

[96] Public Health Service Act § 402(j).

[97] *See Genomics at FDA, available at* http://www.fda.gov/cder/genomics/#genomics (last visited June 17, 2008).

[98] For example, in the past 18 months, at least three IVDMIAs were reviewed by FDA and received 510(k) clearances.

[99] FDCA § 523(c).

[100] FDCA § 702, § 704.

[101] FDCA § 704(g).

highest quality.[102] The CLIA and FDA quality assurance schemes could be harmonized so that the requirements are consistent.

Post Marketing Surveillance and Reporting: Additional information based on actual experience using LDTs for therapeutic decision making would assist in determining which tests have the most value to the health care system. The FDA's authority to impose post-marketing surveillance, medical device reporting, and post-market clinical trials for some LDTs, pursuant to FDCA § 519, § 522, and 21 CFR § 814.82(a)(2), would be beneficial, as would the posting of information on clinical trials used to validate diagnostic tests in the clinical trials registry and results database created by FDAAA, Public Health Service Act § 402(j).

Resources: Prior FDA decisions to exercise less than full-scale regulatory control over LDTs have been based in part on a lack of FDA resources. We recognize that FDA resources may never be sufficient to address all needs. However, since passage of the Medical Device Amendments of 2002, CDRH has been able to increase its staff. Additional 510(k) or PMA submissions will be accompanied by user fees, helping to offset the additional resources FDA would need to devote to this effort. As previously discussed, FDA would be able to use its risk-based classification scheme to reduce or eliminate the regulatory submissions for those LDTs that the FDA determines present little or no patient safety risk.

In sum, FDA has all the scientific expertise and legal authority needed to regulate LDTs, particularly those used in therapeutic decision making.

VI. FDA SHOULD CONCURRENTLY PROCEED WITH RULEMAKING AND ENFORCEMENT ACTIONS

The FDA has never issued an interpretive or substantive rule stating that LDTs are outside of its jurisdiction. Rather, the FDA has consistently taken the position that while FDCA permits regulation of LDTs, because of resource constraints or otherwise, FDA would, in the exercise of its enforcement discretion, not engage in enforcement activities against companies that make LDTs. The FDA is allowed to take a different approach now and should do so, *Syncor Int'l v. Shalala*, 127 F. 3d 90, 94 (D.C. Cir. 1997) (announcement of enforcement approach permits an agency to change its position "even abruptly").[103]

Genentech believes that in cases where an LDT is being offered to guide therapy without strong scientific evidence of analytical and clinical validity, FDA should take immediate enforcement action to remove the test from the market until the clinical laboratory conducts the necessary studies to demonstrate, to FDA's satisfaction, the analytical and clinical validity of

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[102] 21 CFR Part 820 (quality system regulation), *see also* 21 CFR § 862.1660 (quality control material).

[103] An agency is allowed to change course even after engaging in rulemaking so long as it is able to show a reviewing court that the agency recognizes it is changing course, has sound reasons for doing so, and the new action is supported by statute. *Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 41-42 (1983); *Yale-New Haven Hosp. v. Leavitt*, 470 F. 3d 71, 79-80 (2d Cir. 2006).

the test's intended use. The FDA should not delay necessary enforcement action until the completion of rulemaking. Currently, rulemaking is a complex, lengthy process that involves, in addition to FDA, DHHS and the Office of Management and Budget. Therefore, FDA should concurrently take enforcement action against companies that make unwarranted and unsubstantiated claims about LDTs used in therapeutic decision making, and develop appropriate regulations in this area. For the long-term viability of personalized medicine, FDA should initiate rulemaking to establish standards for developing diagnostic tests used to guide therapeutic decision making and state with particularity what information companies must submit to FDA prior to marketing.

Accordingly, Genentech requests that FDA immediately initiate informal notice and comment rulemaking to classify all LDTs that are used either to guide the dose or use of a drug or biologic therapy for a patient as medical devices subject to the existing requirements for medical devices. We further ask that FDA classify those LDTs as Class II or Class III devices using the same standards that it would employ to classify a diagnostic test kit with the same intended purpose.

We also request that FDA immediately announce that its Guidance Document, Pharmacogenetic Tests and Genetic Tests for Heritable Markers,[104] applies to both medical device kits and LDTs. Furthermore, we ask that FDA educate the physician, patient, and payer communities that LDTs that are currently being marketed and sold to guide therapeutic decision making have not received independent review and approval by FDA and are, therefore, are of uncertain validity.

Environmental Impact

The action requested in this Petition will have no environmental impact.

Economic Impact

Genentech believes that FDA regulation of LDTs that are used to make therapeutic decisions for patients will increase the accuracy, reliability, and clinical validity of those tests thereby improving patient care. If patients are treated with optimum doses of the most appropriate drug or biologic, it should lead to less morbidity and mortality and better utilization of scarce health care dollars. In addition, the added costs for preparing and submitting a premarketing application to FDA for an LDT should not be justification to forego appropriate regulatory review, particularly in the interest of protecting patient safety. Any responsible clinical laboratory or company should have already performed the necessary studies to determine analytical and clinical validity of an LDT prior to marketing. Other companies may decide not to attempt to perform the studies knowing that their product is not sufficiently

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[104] *Supra* note 59.

analytically and clinically valid for a critical FDA review. Genentech will submit additional information upon request of the Commissioner.

Certification

The undersigned certifies that, to the best of [his/her] knowledge and believe, this Citizen Petition includes all information and views on which this Petition relies, and it includes all representative data and information known to Genentech which are unfavorable to the Petition.

Sean Johnston

Sean A. Johnston
Senior Vice President and General Counsel