



American
Clinical Laboratory
Association

February 18, 2009

Division of Dockets Management
U.S. Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Comments to Genentech Citizen Petition (Docket ID: FDA-2008-P-0638-001)

Dear Sir or Madam:

The American Clinical Laboratory Association (ACLA) is submitting these comments regarding the Citizen Petition (the “Petition”) filed on December 9, 2008, by Genentech, Inc., (“Genentech”) requesting a change in Food and Drug Administration (FDA) policy on the regulation of *in vitro* diagnostic tests developed and performed by clinical laboratories.¹ ACLA is an association representing clinical laboratories throughout the United States, including local, regional, and national laboratories. ACLA helps promote public awareness about the value of laboratory services in preventing illness, diagnosing disease, assisting in the selection of appropriate medical treatment, and monitoring medical treatment. Many ACLA members create and perform a variety of laboratory-developed tests (LDTs) and have been in the forefront of this rapidly developing and promising area. As a result, ACLA members have a strong interest in, and extensive experience concerning, the issues discussed in the Petition.

I. Executive Summary

ACLA submits this response to the Petition for several related purposes. First, LDTs are important to the welfare and treatment of patients and have played a long-standing role in medical and clinical decision-making—a role that would be undermined by the implementation of the Petition’s requests. In addition, the Petition fails to provide a clear explanation of the request for increased FDA regulatory authority over LDTs, appears not to recognize or understand the complexity of the issues discussed, and is overly broad and, in some cases, inaccurate regarding some of its claims. We address below several incorrect statements made in the Petition, including claims that LDTs are unvalidated and that FDA regulation is necessary to ensure the appropriate oversight of these tests. The Petition also fails to recognize the numerous, well-documented benefits LDTs offer to patients. We provide a detailed discussion of several categories of LDTs and their benefits, including in circumstances in which no FDA-cleared/approved assay currently exists or, in some instances, is likely to be developed. Further, we respond to several allegations about certain LDTs being used in conjunction with Genentech drug products. We also highlight some significant, detrimental policy outcomes that would

¹ Genentech Citizen Petition (filed Dec. 9, 2008), Document ID: FDA-2008-P-0638-001, [available at http://www.regulations.gov/fdmspublic/component/main?main=DocketDetail&d=FDA-2008-P-0638](http://www.regulations.gov/fdmspublic/component/main?main=DocketDetail&d=FDA-2008-P-0638).

result from an FDA decision to accept the Petition's recommendations. Finally, we note the currently unresolved issue of FDA's legal authority to regulate LDTs.

In light of the serious concerns discussed below, ACLA encourages FDA to deny the Petition.

II. Background

LDTs have a well-documented history of providing information that directs the incorporation of the best interventions and the most recent medical advances into patient care, thus enhancing the quality of care and improving outcomes for patients. FDA itself has recognized the benefits of LDTs, explaining in the past that its decision to exercise enforcement discretion in this area was based in part on its recognition that LDTs had "contributed to enhanced standards of medical care in many circumstances and that significant regulatory changes in this area could have negative effects on the public health."² As discussed below, the assertions made in the Petition are, in large part, overly broad, unsupported, and inaccurate. The requests made in the Petition—which, as we discuss further below, are imprecisely phrased and, thus, somewhat difficult to decipher—would have significant and detrimental unintended consequences. To avoid such outcomes, ACLA recommends that FDA deny this Petition. ACLA remains prepared to work with FDA as the agency further refines its position regarding LDTs, and we continue to support the adoption of the regulatory oversight model we have discussed in detail in past meetings with FDA officials. This model is consistent with comments submitted to FDA on the *Draft Guidance for Industry, Clinical Laboratories, and FDA Staff: In Vitro Diagnostic Multivariate Index Assays* ("IVDMIA Draft Guidance," Document ID: FDA-2006-D-0233-0012) and with comments submitted to the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) on its draft report, *U.S. System of Genetic Testing: A Response to the Charge of the Secretary of HHS*.³

III. The Petition Fails to Explain Clearly its Request for Increased FDA Regulatory Authority Over LDTs.

The Petition asks FDA to "require [that] all *in vitro* diagnostic tests intended for use in drug or biologic therapeutic decision making be held to the same scientific and regulatory standards," including both LDTs and device manufacturers' test kits.⁴ As a preliminary matter, we note that although the Petition restricts its call for FDA oversight to only those LDTs "intended for use in drug or biologic therapeutic decision making," this subcategory of LDTs would, as a practical matter, comprise the great majority of LDTs—totaling thousands of tests. Based just on the sheer number of LDTs in this category, it is clear that it would be impossible for FDA, with current resources, to exercise regulatory control in this area. FDA itself has

² 62 *Fed. Reg.* 62242 (Nov. 21, 1997), 62249.

³ ACLA's proposed model is based on interagency coordination and a memorandum of understanding between the Centers for Medicare and Medicaid Services (CMS) and FDA, which would maintain CMS as the lead agency for LDT regulation and would provide FDA with a consultative role. For a more thorough explanation of our proposed model, please see:

<http://www.clinical-labs.org/documents/ACLACommentstoFDAonIVDMIARevisedDraftGuidance.pdf>.

⁴ Genentech Citizen Petition, at 3.

declined to assert jurisdiction over LDTs in the past in recognition of the agency's limited resources.⁵ SACGHS also recognized this resource limitation, observing that “[v]ery few LDTs, however, are reviewed by FDA, and the agency does not currently have sufficient resources to carry out such reviews for all tests if existing review mechanisms are used.”⁶ The restriction described in the Petition appears to suggest that a small subset of LDTs should come under FDA regulatory control, i.e., those LDTs that will be used in drug or biologic therapeutic decision-making. However, reality is otherwise. In fact, the request would cover most LDTs, and FDA simply does not have the resources to manage such a large undertaking.

The Petition, having on the one hand described a limitation or subset of tests to be brought under FDA purview, expresses a different perspective in subsequent discussion—specifically, “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.”⁷ Referring to this second formulation of its request, the Petition asserts that “many LDTs will be considered low risk and would not require significant regulatory oversight,” implying that its request is somewhat narrow in scope.⁸ However, in practice, this would be quite broad—requiring FDA to regulate all LDTs (thousands of tests), first establishing appropriate regulatory status by reviewing all the tests to determine a risk-based classification. It would be a burdensome and complicated task to establish meaningful and appropriate criteria for the risk-based classification of these tests and to apply the appropriate classification (once developed) to thousands of tests.⁹ Significantly, the Secretary's Advisory Committee on Genetic Testing (SACGT), which created a working group in 2000 specifically to develop a methodology and criteria to be used in classifying genetic tests, ultimately concluded a year later that “fundamental, irresolvable questions had been raised about the feasibility of categorizing tests

⁵ See, e.g., Letter from Steve Gutman, Director, Office of *In Vitro* Diagnostic Device Evaluation and Safety (OIVD), Center for Devices and Radiological Health (CDRH), to Peter Levine, President and CEO, Correlogic Systems, Inc. (July 12, 2004), available at <http://www.fda.gov/cdrh/oivd/letters/071204-correlogic.html>. According to Mr. Gutman, “FDA has recognized the skill and expertise of CLIA-regulated high complexity laboratories to use reagents in test procedures and analyses of their own development, and has in general not regulated laboratory-developed testing services. This determination has been based in part upon the need to manage the agency's limited review resources.” *Id.*

⁶ SACGHS, “U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services” (hereinafter “Oversight”) (Apr. 2008), 107, available at http://oba.od.nih.gov/oba/SACGHS/reports/SACGHS_oversight_report.pdf.

⁷ Genentech Citizen Petition, at 3.

⁸ For example, the Petition states, “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.” *Id.* at 4. Similarly, the Petition states, “Genentech's Citizen Petition . . . [s]ubstantiates several patient-focused reasons why all drug tests should be held to the same scientific and regulatory review standards” and “[r]equests that FDA establish regulations governing all LDTs.” *Id.*

⁹ Whereas the Petition asserts that “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,” FDA would still need to make significant resource investments to establish appropriate criteria for such a risk-based classification and to review all LDTs in order to apply these criteria. *Id.* at 29. Thus, the Petition's conclusion that FDA would have adequate resources for this regulation is unfounded.

for oversight purposes based on a limited set of elements in a simple, linear fashion.”¹⁰ Further, SACGT “decided that further efforts to develop a classification methodology for genetic tests should be curtailed for the present.”¹¹

Regardless of what the Petition is asking of FDA—(1) assert jurisdiction over all LDTs and then determine how to regulate each of those LDTs based on a risk-classification analysis or (2) assert jurisdiction over only those LDTs used in drug or biologic therapeutic decision-making—the request has significant problems. Moreover, the imprecision of this request, including the differences highlighted above between the two formulations of the request, demonstrate the complexity of the issues. This inherent complexity, combined with the Petition’s failure to articulate clearly the specific FDA action requested, warrants a very cautious approach by FDA when investigating these issues and considering whether to regulate in this area.¹² Before FDA begins to experiment with any new, untested regulatory approaches, significant and meaningful opportunities should be provided for robust and interactive dialogue with stakeholders, including clinical laboratories, CMS officials involved with implementing the Clinical Laboratory Improvement Amendments of 1988 (CLIA), and representatives of the accreditation and inspection organizations that enforce these requirements on behalf of CMS.

IV. The Petition Overstates the Need for Additional Regulation of LDTs.

The Petition also requests that FDA “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.”¹³ We identify below several ways in which the Petition mistakenly identifies a need for FDA regulation of LDTs. The inaccurate statements and resultant flawed conclusions in the Petition undermine its policy recommendations.

A. There is No History of Significant Problems with LDTs.

The Petition bases its arguments on a belief that the widespread use of LDTs to guide therapy is unsafe for patients under the current regulatory regime.¹⁴ This belief is unsubstantiated by the specific examples cited in its Petition (as discussed below in Section V of this letter) and by the broader evidence of LDT use. In fact, over the past few decades, health care providers have ordered millions of LDTs for their patients with few problems documented

¹⁰ SACGT, “Development of a Classification Methodology for Genetic Tests: Conclusions and Recommendations of the Secretary’s Advisory Committee on Genetic Testing” (Sept. 2001), 11, [available at http://oba.od.nih.gov/oba/sacgt/reports/Addendum_final.pdf](http://oba.od.nih.gov/oba/sacgt/reports/Addendum_final.pdf).

¹¹ Id.

¹² As discussed below in Section VII of this letter, FDA’s authority to assert such jurisdiction over LDTs remains surrounded by legal uncertainty.

¹³ Genentech Citizen Petition, at 5.

¹⁴ For instance, the Petition states, “[w]e believe that an inconsistent application of regulatory oversight of LDTs poses a significant risk to patients.” Id. at 15. Similarly, the Petition notes a concern about “[t]he potential risks to patients when treatment decisions are based on LDTs that lack analytical or clinical validity.” Id. at 6. (Below in this letter we explain why the Petition is wrong to claim that LDTs lack analytical and clinical validity.)

concerning these tests. Specifically with regard to genetic tests, SACGHS has noted that “[t]o date, there have been few documented cases in which patients experienced harm because of errors in a CLIA-regulated genetic test.”¹⁵ While SACGHS also cautioned that “[t]he lack of reports . . . may reflect the absence of a reporting requirement [for adverse events],” even in the absence of a regulatory reporting requirement, litigation or other publicity likely would have revealed more widespread incidence of harm if such harm had, in fact, occurred.¹⁶ While SACGHS cites studies of litigation that identify the few documented cases of harm mentioned, the same source—litigation records—would have revealed significant harm if it had occurred. The absence of such evidence undermines the Petition’s sweeping allegations of the dangers to patients of LDTs.

B. LDTs Are Substantiated in Many Ways, Including by Clinical and Analytical Validation.

The Petition asserts that the clinical validity and analytical validity of LDTs “are not adequately addressed by [CLIA] or voluntary oversight”—an overly broad and inaccurate claim.¹⁷ First, the claim that CLIA “provides limited standards for assessment of analytical validity and virtually no standards for the assessment of clinical validity” is flatly untrue.¹⁸ With regard to analytical validity, the CLIA scheme includes extensive requirements for laboratories to verify or establish tests’ analytical performance characteristics before offering them and reporting patient results based on the tests. Specifically, the CLIA regulations require that before reporting patient test results, all laboratories using unmodified, FDA-cleared or -approved tests must demonstrate accuracy, precision, and reportable ranges of test results for the test systems (meeting performance specifications comparable to those established by the tests’ manufacturers), and must verify that the manufacturers’ reference intervals are appropriate for the laboratories’ patient populations.¹⁹ Further, the CLIA regulations require laboratories that modify FDA-cleared or -approved tests, that use LDTs, or that use test systems for which the manufacturers do not provide performance specifications, to establish the following performance characteristics before reporting patient test results: accuracy; precision; analytical sensitivity; analytical specificity to include interfering substances; reportable range of test results for the test system; reference intervals (normal values); and any other performance characteristic required for test performance.²⁰

With regard to clinical validity, the Petition’s assertion is also far too harsh. The CLIA regulations currently require laboratory directors to ensure that “[t]he test methodologies selected have the capability of providing the quality of results required for patient care.”²¹ Tests can have the “capability of providing the quality of results required for patient care” only if they are clinically relevant for the patient populations being tested (i.e., are clinically valid). The CLIA

¹⁵ SACGHS, “Oversight,” at 32.

¹⁶ Id.

¹⁷ Genentech Citizen Petition, at 6.

¹⁸ Id. at 6, note 7.

¹⁹ 42 C.F.R. § 493.1253(b)(1).

²⁰ Id. at (b)(2).

²¹ 42 C.F.R. §§ 493.1407(e)(3)(i), 493.1445(e)(3)(i).

statute provides that “[t]he Secretary shall issue standards to assure consistent performance by laboratories issued a certificate under this section of *valid* and reliable laboratory examinations and other procedures.”²² To the extent that Genentech (or any other stakeholder) has concerns about the CLIA standards for assessment of clinical validity, the appropriate solution is to bring these concerns to CMS and petition the agency to make clarifications through the CLIA Interpretive Guidelines²³ or amendment of the CLIA regulations²⁴—not to ask FDA to impose on LDTs a completely new regulatory scheme.

Other aspects of current laboratory regulation also address clinical validity. The clinical and analytical validity of LDTs are reviewed by the College of American Pathologists (CAP) and some State agencies. CAP, which has been authorized by CMS to accredit laboratories as meeting CLIA requirements, runs its Laboratory Accreditation Program with the goals of “ensur[ing] that tests are analytically and clinically valid, that there is patient safety and patient access to testing, and that there is innovation and improvement of LDTs.”²⁵ Currently, roughly 6,000 laboratories in the United States are CAP-accredited, and 23,000 laboratories are enrolled in the CAP proficiency testing programs.²⁶ The CAP Laboratory Accreditation Program covers the “complete array of disciplines and testing procedures available” in laboratories, and the CAP Laboratory Accreditation Standards used in the program are applied through “checklist” questions, which “constantly evolve to reflect changes in technology and are tailored specifically to the size and scope of individual laboratories.”²⁷ Further, CAP provides mechanisms in its Laboratory Accreditation Program for assuring both the clinical and analytical validity of LDTs.²⁸ CAP uses checklists and laboratory inspections to evaluate the analytical validity of assays that have been made available²⁹ and expects laboratories using LDTs to demonstrate how the tests they offer have been clinically validated.³⁰ CAP-accredited laboratories that fail to

²² 42 U.S.C. § 263a(f)(1) (emphasis added).

²³ See CMS, “Appendix C: Survey Procedures and Interpretive Guidelines for Laboratories and Laboratory Services,” available at <http://www.cms.hhs.gov/CLIA/downloads/apcpolicy.pdf> (last visited Jan. 19, 2009).

²⁴ See 42 C.F.R. § 493.1, *et seq.*

²⁵ See SACGHS, “Oversight,” at 47.

²⁶ CAP Fact Sheet, available at

http://www.cap.org/apps/cap.portal?nfpb=true&cntvwrPtl_t_actionOverride=%2Fportlets%2FcontentViewer%2Fshow&_windowLabel=cntvwrPtl&cntvwrPtl%7BactionForm.contentReference%7D=media_resources%2Ffactsheet.html&_state=maximized&_pageLabel=cntvwr (last visited Jan. 15, 2009).

²⁷ *Id.*

²⁸ See, CAP, *Laboratory Accreditation Manual* (July 2007), available at

http://www.cap.org/apps/docs/laboratory_accreditation/standards/lapmanual_0707.pdf.

²⁹ As explained by SACGHS, “[t]he analytical validation must include an evaluation of the performance characteristics such as analytical sensitivity, analytical specificity, precision, linearity (for quantitative tests), reportable range of patient test results, reference range (normal values), and any other applicable performance characteristic.” SACGHS, “Oversight,” at 105. See also 42 C.F.R. § 493.1253(b); CAP, “Molecular Pathology Checklist” (2007), available at

http://www.cap.org/apps/docs/laboratory_accreditation/checklists/molecular_pathology_sep07.pdf.

³⁰ To evaluate the sufficiency of the documentation for the performance characteristics of an LDT, CAP “determines whether clinical performance characteristics of each assay are documented, using either literature citations or a summary of internal study results, and whether final reports include an appropriate summary of the methods, the loci or mutations tested, the analytical interpretation, the clinical interpretation (if appropriate), and a

make such demonstrations are subject to loss of accreditation or other sanctions, contrary to the Petition's assertion that "[v]oluntary professional organizations . . . have no enforcement authority and thus offer limited public health protection."³¹

State-level regulation of laboratory testing services is also important. As SACGHS has noted, 26 States have statutory authority to oversee the practice of clinical laboratory medicine, and CMS has exempted Washington and New York from CLIA owing to the agency's determination that the review standards employed by these two States are equivalent to, or stricter than, the CLIA statute and regulations. Washington reviews some tests for clinical validity, and New York reviews all non-FDA-approved tests (including LDTs) for both analytical and clinical validation before they can be offered in the State.³² Importantly, the New York law covers all tests performed on New York residents, no matter where the tests are performed. It is likely that all reference laboratories in the United States are licensed by New York. Moreover, "[i]t has been estimated that 75 percent of the genetic testing in the United States is subject to New York State oversight."³³ Significant New York regulation, which includes both analytical and clinical validity, along with the substantial CAP and CLIA review processes, makes the reality a far cry from the assertions made in the Petition about the lack of independent review of the clinical and analytical validity of LDTs.

Furthermore, contrary to the Petition's sweeping and unsupported statements about the ineffectiveness or lack of validation of certain enumerated LDTs,³⁴ there is, in fact, a significant body of evidence supporting these tests. This evidence, available on the companies' websites, includes peer-reviewed journal articles, presentations, and abstracts, all of which support the tests' clinical validity, medical decision impact, platform technology, assay development, and clinical trials.³⁵ Because peer-reviewed literature is a well-respected source of information in the

summary statement, signed by the laboratory director or designee, that documents the review of validation studies and approval of the test for clinical use." SACGHS, "Oversight," at 105.

³¹ Genentech Citizen Petition, at 6, note 7.

³² SACGHS, "Oversight," at 35, 36.

³³ *Id.* at 36, 37. We note that the New York requirements for validation review apply to non-genetic as well as genetic tests, though we have not located a parallel estimation of the percentage of all non-genetic tests, or of all tests, subject to New York regulation.

³⁴ For instance, the Petition asserts that "[t]he 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." Genentech Citizen Petition, at 6.

³⁵ See, e.g., Genomic Health, Inc., "What's been published/presented?," available at <http://www.oncotypedx.com/HealthcareProfessional/Publications.aspx> (last visited Jan. 19, 2009) (containing scientific publications and presentations relating to *Oncotype DX*, a breast cancer assay); Monogram Biosciences, Inc., "Classify HER2 status with a new level of confidence," available at http://hermarkassay.com/reclassify_her2_status.aspx (last visited Jan. 19, 2009) (providing links to a variety of clinical studies and publications regarding the HERmark Assay, a breast cancer assay); and Quest Diagnostics, "UGT1A1 Gene Polymorphism (TA Repeat)," available at http://questdiagnostics.com/hcp/intguide/jsp/showintguidepage.jsp?fn=TS_UGT1A1.htm (last visited Jan. 19, 2009) (providing numerous references to scientific articles reviewing a test for the *UGT1A1* gene).

medical community, the Petition is incorrect to assert that claims about clinical and/or analytical validity are of “unknown” worth when not reviewed by FDA.³⁶

Finally, to the extent that a decision is ever made that CLIA should focus more directly on clinical validity, the New York and CAP models, discussed above, demonstrate how that could be accomplished. The New York and CAP systems have a great deal of experience in reviewing the clinical validity of LDTs, and this experience would provide a valuable and appropriate framework for considering any changes to the CLIA regulatory scheme. Further, modifying CLIA, as opposed to imposing a new FDA regulatory framework on clinical laboratories, would be the simplest and best way to address any identified need to strengthen the review of clinical validity currently conducted under CLIA. The benefits of retaining the CLIA framework—and the many concerns about imposing FDA requirements on LDTs—are discussed in more detail in Section VI below.

C. FDA Approval is Not the Only Way to Ensure the Appropriate Oversight of Tests.

The Petition asserts that there are “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”³⁷ and, further, that “[t]he potential risks to patients when treatment decisions are based on LDTs that lack analytical or clinical validity are not adequately addressed by the [CLIA] or voluntary oversight.”³⁸ According to the Petition, these risks make it “imperative that FDA expand its regulatory reach over such tests to ensure that any such claims made are scientifically and clinically proven.”³⁹ Despite the fervor with which these assertions are made, the central premise and, therefore, the conclusion are flawed.

The Petition asserts that LDTs are being used “without any assurance that the claims being made about these tests are analytically or clinically valid”⁴⁰; this is simply not true. As discussed above, LDTs are, in fact, subject to both clinical and analytical validation requirements under CLIA as well as under State and CAP requirements. The success of these regulatory mechanisms over time has been demonstrated by the countless benefits LDTs have provided to patients (discussed in detail in Section V below) and the sparse litigation record, which, as also discussed above, would be expected to have documented significant danger of LDT use if this were, in fact, a legitimate concern. The Petition fails to recognize the successes of the existing regulatory structure, the benefits of LDTs, and the lack of documented harm from LDTs, all of which together contradict the Petition’s conclusion that FDA review is necessary to “ensure that any such claims made [by laboratories about LDTs] are scientifically and clinically proven.”⁴¹

³⁶ Genentech Citizen Petition, at 6.

³⁷ *Id.* at 15.

³⁸ *Id.* at 6.

³⁹ *Id.* at 15.

⁴⁰ *Id.* at 7.

⁴¹ *Id.* at 15.

V. The Petition Makes Inaccurate Statements about the Specific LDTs it Discusses and Fails to Recognize Many Other Established, Beneficial LDTs.

The Petition fails to acknowledge the benefits of LDTs to patients, which are many, varied, and critical to important advances in patient care. Accordingly, in Subsection A below, we discuss the numerous ways that LDTs benefit patients, providing a variety of examples of such tests (many of which are well-established and well-accepted in the medical community). However, the Petition does discuss some examples of LDTs it views as problematic. These LDTs include those used to determine whether patients should be treated with Herceptin® (trastuzumab), Rituxin® (rituximab), Avastin® (bevacizumab), and Tarceva® (erlotinib)—drugs manufactured by Genentech. According to the Petition, “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.”⁴² In Subsection B below, we identify some ways in which the Petition mischaracterizes each of the LDTs it alleges are being used improperly and without clinical or analytical validation.

A. The Petition Fails to Recognize the Significant Patient Care Benefits Available through Numerous, Well-Established LDTs.

A decision to modify the regulatory paradigm for LDTs must take into account, among other things, the numerous ways in which LDTs are and have been instrumental to good patient care and well-accepted by the medical community. In this subsection, we provide several examples of LDTs that demonstrate the ability of clinical laboratories to incorporate medical innovations quickly and effectively into patient care services, provide rapid responses to disease outbreaks, and provide treatment guidance for patients with rare diseases or in other situations in which, for any number of reasons, no FDA-cleared or -approved tests exist. Importantly, many of the tests discussed below (and many other LDTs not specifically mentioned) are well-established as standards of care in practice guidelines issued by major professional groups and are reducing wasteful expenditures attributable to population-wide treatment approaches that these tests are rendering obsolete. These examples are meant to highlight some benefits of LDTs, not to provide an exhaustive list of beneficial tests. This discussion also is intended to emphasize that these benefits are available because of the flexibility afforded to laboratories under CLIA to incorporate medical advances quickly into LDTs—flexibility that would be lost under the FDA regulatory scheme requested in the Petition.

The examples discussed below in this subsection include the following:

- DNA Sequencing Assays;
- Karyotype/Chromosome/Cytogenetic Analyses;
- Newborn Screening Tests;
- HIV Viral Load Testing and Resistance Testing;
- Tests Used to Control Outbreaks of Infectious Diseases;

⁴² *Id.* at 7.

- Tests for Low-Incidence Diseases; and
- Tests that Are Part of Standard Recommended Care.

Each of these categories of tests includes LDTs that provide significant benefits to patients in the absence of any FDA-cleared or -approved tests.

1. DNA Sequencing Assays

A number of DNA sequencing assays—all LDTs—for several genetic tests are widely used and respected in the medical community. These include, for example, the sequencing assays for hemoglobinopathies, Tay-Sachs disease, Gaucher disease, Canavan disease, Niemann Pick disease, multiple endocrine neoplasia, hereditary nonpolyposis colon cancer (HNPCC), breast cancer, and hereditary deafness. There are no FDA-approved or -cleared DNA sequencing assays, and the LDTs in this category are very important medically. In fact, the American College of Medical Genetics' (ACMG) Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group recently issued a recommendation statement regarding the testing for Lynch syndrome/HNPCC (which can include DNA sequencing) in diagnosis and decision-making for family members with risk for colon and other cancers. The EGAPP Working Group “found sufficient evidence to recommend offering genetic testing for Lynch syndrome to individuals with newly diagnosed colorectal cancer to reduce morbidity and mortality in relatives” and “concluded that there is moderate certainty that such a testing strategy would provide moderate population benefit.”⁴³

2. Karyotype/Chromosome/Cytogenetic Analyses

Karyotype/chromosome/cytogenetic analyses, such as those used to detect leukemia/lymphoma, developmental delay/mental retardation, and fetal aneuploidy, are currently offered only through LDTs (not FDA-approved/cleared kits). These LDTs provide significant medical benefits to patients who are diagnosed through these tests and then can begin receiving appropriate treatment, as well as to parents who can receive important information about their unborn children that can help them prepare for the births of children with special medical needs. Most reagents used in chromosome testing are considered “general purpose reagents,” which are chemical reagents that are not FDA-approved/cleared but that are widely used in laboratories to help culture cells whose chromosomes can then be analyzed. Similarly, the widely-accepted and, in many cases, long-standing culture methods for microbiology and virology applications also use these general purpose reagents. For example, throat culture samples taken in physicians' offices of patients presenting with symptoms of Strep throat are sent to laboratories, which use general purpose reagents to determine whether the Streptococcus bacterium (i.e., the cause of Strep throat) is present. This is a very standard LDT that has been used successfully for years. Numerous other swab tests are commonly done and sent to laboratories for culture, including tests for a variety of viruses, bacteria, and fungal infections.

⁴³ EGAPP Working Group, “Recommendations from the EGAPP Working Group: genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives” ACMG, *Genetics in Medicine*, Vol. 11, No. 1 (Jan. 2009), 35-41, at 35.

3. Newborn Screening Tests

The many LDTs used to test newborns for inborn errors of metabolism (such as phenylketonuria, commonly known as PKU) play an essential role in ensuring that treatment is started as early as needed to minimize complications and avoid preventable problems associated with these metabolic disorders. These LDTs include, for example, urine organic acid analysis, plasma and urine amino acids analysis, and plasma acylcarnitine profile. Many States require newborn screening tests for specified conditions (which vary by State). ACMG, pursuant to its commission by the Maternal and Child Health Bureau of the Health Resources and Services Administration of the U.S. Department of Health and Human Services (HHS), has conducted a scientific analysis of the benefits of numerous newborn screening tests and has provided recommendations for standardizing outcomes and guidelines for State newborn screening programs.⁴⁴ As ACMG noted in its report, “it is estimated that about 1 in every 800 newborns in the United States—or 5,000 of 4.1 million newborns each year—is born with a potentially severe or lethal condition for which screening and the treatment for the prevention of many or all of the complications of the condition are available.”⁴⁵ Tests used in newborn screening, including the LDTs mentioned above, are critical in facilitating the provision of these essential health care services, and there are no FDA-cleared/approved assays for most of these newborn screening tests.

4. HIV Viral Load Testing and Resistance Testing

A classic example of the way in which LDTs can translate medical innovations into patient care services in a safe and timely fashion is HIV viral load and resistance testing. HIV viral load testing, also called HIV quantitative RNA testing, determines the amount of virus in a patient’s blood, and HIV resistance testing, also called HIV phenotype/genotype testing, determines the efficacy of a specific drug for a particular patient. These two types of testing are done in conjunction with one another. First, the HIV viral load test determines whether the drug a patient has already been using has been effective for that patient by reducing viral load. Second, if the patient’s drug regimen is shown to have been unsuccessful, then the HIV phenotype/genotype test can determine why that regimen has not been effective. Moreover, HIV genotype/phenotype tests can be used to determine the efficacy for particular patients of new drugs as they become available. This determination needs to be made as rapidly as possible, since patients with HIV easily can become resistant to their current medications, and determining quickly whether they could be treated effectively by new drugs could prolong their lives or avoid significant complications.

HIV viral load testing was first made available as an LDT around 1989-90, a few years before the first pre-market approval application was submitted to FDA and roughly six or seven years before FDA approved a kit to determine progression of disease in July 1996. Thus, even before any FDA-approved/cleared assays existed, clinical laboratories conducting HIV viral load testing, in conjunction with HIV resistance testing, were providing much-needed patient care

⁴⁴ Michael S. Watson, et al., “Newborn Screening Main Report,” ACMG, *Genetics in Medicine*, Vol. 8, No. 5, Supplement (May 2006), 12S-252S.

⁴⁵ *Id.* at 15S.

services, and their LDTs have served as the basis for the development of combination therapy and the approval of new antivirals. Moreover, even though there are now FDA-approved/cleared HIV viral load and resistance assays on the market, manufacturers cannot incorporate medical advances into these assays in a time-sensitive manner owing to the lengthy FDA approval/clearance processes, which means that only through the LDT versions can medical advances reach patients timely.

5. Tests Used to Control Outbreaks of Infectious Diseases

Another key advantage LDTs have over FDA-cleared/approved tests is their ability to respond in real time to disease outbreaks. Many clinical laboratories track world trends regarding infectious diseases and, in some cases, work directly with HHS' Centers for Disease Control and Prevention (CDC) to develop tests for potentially devastating infectious diseases, such as SARS and Avian Influenza. These laboratories are poised to offer these tests if an outbreak of one of these diseases ever occurs. This immediate or near-immediate response time is critical given the immense destruction possible through an uncontained outbreak of the deadliest infectious diseases. In such an emergency situation, waiting for manufacturers to develop tests and go through all the FDA approval/clearance processes would take far too long. The FDA review process is simply not nimble enough to allow appropriate, timely response to infectious disease outbreaks, whereas the CLIA system enables laboratories to be prepared to provide life-saving help if the situation arises.

6. Tests for Low-Incidence Diseases

Yet another way in which LDTs provide significant patient care benefits in the absence of FDA-approved or -cleared assays is by offering tests for rare diseases. This category of tests includes tests for diseases that are of relatively low incidence in the United States, such as the LDTs used in Ashkenazi Jewish screening (i.e., tests for Tay-Sachs disease, Canavan disease, Cystic Fibrosis, and Familial Dysautonomia).⁴⁶ This category also includes LDTs for a variety of very rare diseases, often called "orphan diseases," such as the tests for herpes simplex encephalitis, muscular dystrophies (Duchenne, Becker, limb-girdle, etc.), hereditary hemochromatosis, Prader-Willi/Angelman syndromes, neurofibromatosis (types 1 and 2), and congenital adrenal hyperplasia. Manufacturers are often reluctant to invest the resources to run trials and seek FDA approval or clearance for tests for these orphan diseases. For instance, the test for herpes simplex encephalitis, which detects herpes simplex viral DNA in cerebrospinal fluid, is used to make a critical diagnosis needed for specific treatment—and is available only as an LDT. There are no FDA-approved/cleared kits and no economic incentives for a manufacturer to go through the expensive and time-consuming FDA approval/clearance processes for a low-use test, much less one that requires cerebrospinal fluid as a sample. Owing

⁴⁶ Carrier screening for Ashkenazi Jewish disorders is recognized in well-respected, peer-reviewed literature and is recommended by the American College of Obstetricians and Gynecologists (ACOG) for individuals of Eastern European Jewish descent. See ACOG Committee on Genetics, "Prenatal and Preconceptional Carrier Screening for Genetic Diseases in Individuals of Eastern European Jewish Descent," Committee Opinion No. 298 (Aug. 2004). See also, Charles M. Strom, et al., "Molecular screening for diseases frequent in Ashkenazi Jews: Lessons learned from more than 100,000 tests performed in a commercial laboratory," *ACMG, Genetics in Medicine*, Vol. 6, No. 3 (May/June 2004), 145-152.

to the lack of incentives for manufacturers to develop FDA-approved/cleared tests for these types of diseases, clinical laboratories are filling in a significant gap for individuals who have one or more of these rare diseases.

7. Tests that are Part of Standard Recommended Care

A good example of LDTs that are part of standard recommended care in the absence of any FDA-approved/cleared tests are the tests involved in the evaluation of children with developmental delay/mental retardation. The standard of care for this evaluation is to conduct Fragile X Syndrome testing (since Fragile X Syndrome is one cause of mental retardation) and chromosome analysis (to identify other causes of mental retardation).⁴⁷ LDTs are available for both chromosome analysis and Fragile X testing and are widely used. For Fragile X Syndrome testing, there is one research-use-only (RUO) assay available, but no FDA-approved or -cleared tests are available for use in diagnostic procedures. There are, however, a number of LDTs well-established for use in Fragile X Syndrome testing, as documented in one recent study coordinated by the CDC and the Association for Molecular Pathology.⁴⁸ This study compared the performance of several laboratories using their LDTs to evaluate the same set of reference materials, as well as the National Institute of Standards and Technologies' standard reference materials, and found that all of these assays performed well.⁴⁹

B. The Petition Makes Inaccurate Representations about LDTs Used in Connection with Genentech's Drugs.

The Petition asserts that several LDT manufacturers are "making claims about their test(s)" related to Genentech products "without collaboration or consultation with Genentech" and without FDA approval.⁵⁰ In what follows, we point out specific flaws in the Petition's assertions about each of the named LDTs used in conjunction with Genentech drug products.

1. Herceptin® (trastuzumab)

The Petition states that Herceptin's FDA-approved label identifies several FDA-approved tests that can be used to determine whether Herceptin would be an appropriate therapy for a given patient. The Petition further notes that 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."⁵¹ Specifically, the Petition singles out Combimatrix Molecular Diagnostics'

⁴⁷ See Stephanie Sherman, Beth A. Pletcher, and Deborah A. Driscoll, "Fragile X syndrome: Diagnostic and carrier testing," *ACMG, Genetics in Medicine*, Vol. 7, No. 8 (Oct. 2005). See also Robert A. Saul and Jack C. Tarleton, "FMR1-Related Disorders," *GeneReviews* (updated Aug. 5, 2008), available at <http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=fragilex>.

⁴⁸ Jean Amos Wilson, et al., "Consensus Characterization of 16 *FMR1* Reference Materials: A Consortium Study," *Journal of Molecular Diagnostics*, Vol. 10, No. 1 (Jan. 2008).

⁴⁹ *Id.*

⁵⁰ Genentech Citizen Petition, at 7.

⁵¹ *Id.* at 8.

LDT, the HerScan™ test, which is used to detect amplification of the *HER-2* gene in early breast cancer, and Monogram Biosciences' breast cancer assay, HERmark™, used to identify *HER-2* protein expression. The Petition states that “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.”⁵² As we have stated previously in these comments, the Petition consistently and inaccurately portrays FDA review as the sole method of evaluating clinical (and analytical) validity, thus drawing the false conclusion that claims about non-FDA-cleared or -approved tests, such as HerScan and HERmark, are *de facto* unsupportable.

Further, the Petition expresses concern that claims by Monogram Biosciences that “HERmark is a CLIA validated assay processed at Monogram Sciences [sic] a CAP-certified central laboratory”⁵³ and that “the HERmark assay is fully approved”⁵⁴ could “confuse physicians and patients and lead them to believe that the assay has been validated and approved for use by FDA.”⁵⁵ As a preliminary matter, we point out that the Petition has taken the second statement out of the context of the discussion on the Q4 2007 earnings call during which the statement was made. During this call, immediately after Bill Young, CEO of Monogram Biosciences, Inc., described HERmark as “fully approved,” he said: “In December 2007, we have received confirmation from the College of American Pathologists that the HERmark assay is certified for routine patient testing in our CLIA Certified Clinical Reference Laboratory.”⁵⁶ These two sentences read together, as they were intended to be, do not suggest that the HERmark test is FDA-approved, but rather specify that Monogram Biosciences had been certified by CAP under CLIA. Likewise, the first statement above, which appears on Monogram Biosciences' website, is confined to claims about CLIA and CAP. Concerns about patient or physician confusion (if any such confusion exists) should be addressed by encouraging CMS and/or FDA to improve communications to patients and physicians about the meaning of terms like “CLIA-validated,” “CAP-accredited,” “FDA-cleared,” and “FDA-approved”—not by suggesting that laboratories are creating confusion by accurately using existing terminology.

2. Rituxan® (rituximab)

The Petition also discusses PGxPredict™:RITUXIMAB, an LDT offered by Clinical Data to predict the likelihood that patients with follicular non-Hodgkin's lymphoma will respond to rituximab. The Petition cites claims made by Clinical Data in a press release announcing the test and on the company's website. According to the Petition, “[i]n 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

⁵² Id.

⁵³ Id. (quoting Monogram Biosciences, Inc., “HERmark Assay Features & Benefits,” available at http://hermarkassay.com/hermark_features.aspx (last visited Jan. 19, 2009).

⁵⁴ Id. at 9 (quoting Monogram Biosciences, Inc., “Q4 Earnings Call Transcript” (Feb. 7, 2008), available at <http://seekingalpha.com/article/64947-monogram-biosciences-inc-q4-2007-earnings-call-transcript?page=-1>).

⁵⁵ Id.

⁵⁶ Monogram Biosciences, Inc., “Q4 Earnings Call Transcript” (Feb. 7, 2008), 3, available at <http://seekingalpha.com/article/64947-monogram-biosciences-inc-q4-2007-earnings-call-transcript?page=-1>.

physician.”⁵⁷ Contrary to the Petition’s contention, the Clinical Data website contains references to scientific articles published in peer-reviewed journals, demonstrating that there has, in fact, been independent review of the company’s claims about the test.⁵⁸ The Petition also indicates that Genentech is, “concerned that these clinically unvalidated claims may result in inappropriate use of Rituxan as a therapy.”⁵⁹ As stated above, the claims are not clinically unvalidated.

3. Avastin® (bevacizumab)

Included in the Petition’s list of LDTs designed to guide treatment regarding Genentech drug products is Rosetta Genomics’ test to differentiate squamous from non-squamous non-small cell lung cancer (miRview™ squamous), which is designed to guide treatment decisions with respect to Avastin and/or bevacizumab. The Petition expresses concern that Rosetta Genomics has made clinical claims about the usefulness of its test in guiding drug treatment decisions without obtaining FDA clearance or approval or indicating that “it intends to seek FDA review of this test.”⁶⁰ The Petition asserts that “no independent verification has been made of [Rosetta Genomics’] 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.”⁶¹ Rosetta Genomics’ website contains numerous references to scientific articles and presentations supporting the use of miRview squamous as a diagnostic tool, and contrary to the Petition’s claim that the test has “no independent verification,” many of these articles were published in peer-reviewed journals.⁶² Once again, the Petition seems to recognize only FDA review as a reliable means of ensuring clinical and analytical validity of LDTs, but this assumption is unwarranted, as discussed above.

4. Tarceva® (Erlotinib)

The Petition notes that clinical laboratories are currently offering LDTs to detect mutations of the epidermal growth factor receptor and *K-ras* gene (*KRAS*) and that some studies have suggested that such mutations could affect the receptivity of lung cancer patients to Tarceva, a Genentech product. These LDTs include Genzyme Genetics’ *KRAS* Mutation Analysis, intended to be used for patients with colorectal cancer, non-small cell lung cancer, and other types of cancer, and Response Genetics’ ResponseDX™: Lung and ResponseDX: Colon, intended to help determine patients’ response to erlotinib and other drugs, including gefitinib, gemcitamine, and fluoropyrimidine-based therapies. While the Petition cites certain information from these companies’ websites regarding their tests, it does not raise any specific concerns

⁵⁷ Genentech Citizen Petition, at 10.

⁵⁸ See, e.g., PGx Health, “Frequently Asked Questions,” available at <http://www.pgxhealth.com/genetictests/rituximab/physicians/faq.cfm> (last visited Jan. 19, 2009); Clinical Data Press Release, “Clinical Data Launches PGxPredict:RITUXIMAB on Schedule” (Jan. 30, 2007), available at <http://investor.clda.com/releasedetail.cfm?releaseid=227577>.

⁵⁹ Genentech Citizen Petition, at 10.

⁶⁰ *Id.* at 11.

⁶¹ *Id.* at 12.

⁶² Rosetta Genomics, “miRview squamous: References,” available at http://www.rosettagenomics.com/inner.asp?first_tier=126&second_tier=127&third_tier=140 (last visited Jan. 19, 2009).

about the tests or the claims made about them on these websites. Furthermore, the American Society of Clinical Oncology recently released a provisional clinical opinion recommending that “all patients with metastatic colorectal carcinoma who are candidates for anti-EGFR antibody therapy should have their tumor tested for *KRAS* mutations in a CLIA-accredited laboratory” and that treatment decisions should be based on the results of these tests.⁶³ There are currently no FDA-cleared/approved assays for this test, though the test has now been given preliminary support from an important professional organization for oncological clinicians.

VI. The Petition’s Recommendations Would Produce Serious, Detrimental Policy Outcomes.

As discussed above, the Petition makes many inaccurate and/or overly broad statements and fails to recognize the many benefits of LDTs. The Petition also fails to acknowledge the many advantages of retaining CLIA as the regulatory mechanism—and CMS as the lead regulatory agency—responsible for assuring quality of clinical laboratory testing services, including LDTs. This section addresses the ways in which granting the requests of the Petition would result in poor public policy.

A. Implementing the Petition’s Requests Would Stifle Much-Needed Innovation and Undermine the Ability of Laboratories, through LDTs, to Bring the Latest Medical Advances to Patients Expeditiously.

With the growth of personalized medicine, we are entering an era that will allow specialized clinical laboratories to analyze a cancer patient’s tissue or blood and determine the source of cancer, how likely it is to recur, and the treatment options that are best suited for the patient. These benefits of LDTs are substantial, though not reflected in the Petition. But the Petition’s recommendations—i.e., that FDA expand its regulatory authority over LDTs through rulemaking and begin enforcement actions against certain LDTs even before rulemaking is completed—would undermine the ability of LDTs to continue offering these tremendous benefits to patients. Specifically, the Petition’s proposed approach would inhibit innovation and the application of new advances in testing, just at the time when there is such potential in the areas of personalized medicine and genetic testing.

If FDA were to adopt a policy requiring FDA preclearance or preapproval of LDTs before a laboratory could commercially offer the test, then the ability to innovate quickly—that important public health “safety valve” offered by LDTs that was the basis for FDA’s prior policy—would disappear. This would have a profound, negative impact on health care delivery and the practice of medicine. For example, the ability and flexibility that various laboratories (including those in academic institutions) have to respond to emerging medical needs enable those laboratories to offer services that would never generate the financial and operational returns necessary to allow broad commercial introduction of an *in vitro* diagnostic test kit. In

⁶³ Carmen J. Allegra, et al., “American Society of Clinical Oncology Provisional Clinical Opinion: Testing for *KRAS* Gene Mutations in Patients with Metastatic Colorectal Carcinoma to Predict Response to Anti-Epidermal Growth Factor Receptor Monoclonal Antibody Therapy,” American Society of Clinical Oncology (Jan. 2009).

many cases, no *in vitro* diagnostic device manufacturer will ever manufacture a kit for such tests. If all laboratories were required to clear their tests with FDA, then many tests simply would not be made available by laboratories, just as they are not offered by any kit manufacturer.

In addition, other tests with broader application also would find it difficult to make their way to market. As HHS' recent report on personalized medicine notes, "[v]enture capital will likely remain the primary source of financing for young innovators in this space [i.e., personalized medicine] due to the extraordinary risk associated with investing in healthcare technologies."⁶⁴ As the HHS report also indicates, small changes in regulatory policies and reimbursement outlook can have a direct impact on the ability of emerging firms to attract the necessary investment.⁶⁵ The emergence of significant new barriers to entry into this market, in the form of new FDA premarket requirements and the accompanying costs, almost certainly would make it more difficult to attract the needed investment. As a result, the ability of these new companies to succeed would be impeded significantly.

Indeed, investors who have funded innovators in the IVDMA field, in particular, have made it clear that they will not continue to invest in personalized medicine if FDA's IVDMA Draft Guidance is finalized and the burdens of FDA clearance or approval are imposed on laboratories consistent with the way FDA currently regulates *in vitro* diagnostic test kit manufacturers. Likewise, innovators offering personalized medicine tests have indicated that they will discontinue development programs extending into new clinical conditions and will significantly curtail operations if FDA finalizes the IVDMA Draft Guidance. This would result in a loss of jobs and a substantial reduction of the economic presence of these companies in their communities. To the extent that many of these innovations start in the research laboratories of major academic medical centers and are then sources of income (from royalties collected on the intellectual property licensed to a laboratory that develops its own LDT based on that intellectual property), it is reasonable to predict the loss of financing of such research and the loss of highly skilled people to other enterprises. The impact also would extend to the loss of tests that can help direct physicians to more appropriate therapy selection—including many of the types of tests discussed above in Section V of these comments. Without these tests, the promise of personalized medicine to provide more effective, safer, and more cost-effective care will not be realized.

These substantial, adverse outcomes have increased significance in light of the recent trend, identified by FDA, that fewer new therapies (both drugs and medical devices) are being brought to market to benefit patients than in the past.⁶⁶ Specifically, FDA has indicated that, for a number of reasons, "novel therapies are not moving through development and to patients as quickly as they could be," citing to a recent study showing that "in 2004, we hit an all time low

⁶⁴ HHS, *Personalized HealthCare: Pioneers, Partnerships, Progress*, (Nov. 2008), 129, available at http://www.hhs.gov/myhealthcare/news/phc_2008_report.pdf.

⁶⁵ *Id.* at 130.

⁶⁶ According to FDA, "[d]uring the last several years, the number of new drug and biologic applications submitted to FDA has declined significantly; the number of innovative medical device applications has also decreased." FDA, *Challenge and Opportunity on the Critical Path to New Medical Products* (hereinafter "*Challenge*") (Mar. 2004), i, ii, available at <http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.pdf>.

for the past 20 years worldwide in the number of new medical therapies reaching the market.”⁶⁷ FDA has also observed that “the applied sciences needed for medical product development have not kept pace with the tremendous advances in the basic sciences. The new science is not being used to guide the technology development process in the same way that it is accelerating the technology discovery process.”⁶⁸ To address these concerns, FDA launched its Critical Path Initiative in 2004 “with the goal of promoting efficient development of safe and effective new medical treatments” and increasing the speed with which “innovative medical therapies reach[] patients.”⁶⁹ Importantly, LDTs are continuously incorporating the most cutting-edge medical advances for the benefit of patients, thus accomplishing the Critical Path Initiative’s goal. By removing the ability of LDTs to translate medical advances into important and beneficial patient care rapidly, implementing the requests of the Petition actually would undercut the goals of FDA’s Critical Path Initiative.

B. The Petition Overlooks the Advantages of Maintaining the Current CLIA Regime.

In addition to identifying the significant drawbacks the Petition’s proposed regulatory approach for LDTs would have for patient care, it is important to emphasize the benefits of maintaining the existing regulatory scheme for these tests—under CLIA. Specifically designed by Congress to regulate clinical laboratories, CLIA is a comprehensive set of rules that CMS has implemented through extensive regulations, which ensure the accuracy and reliability of laboratory tests. All laboratories certified under CLIA must meet specified standards in the areas of proficiency testing, quality assurance, patient test management, and personnel. Accordingly, there is already an existing regulatory and compliance framework to which clinical laboratories are subject.

Over the past 20 years, CLIA has regulated the quality of clinical laboratory testing services, facilitated innovation, and protected patients. CLIA also has helped to usher numerous tests to market, both safely and timely, that might not have reached the market under an FDA regime because of the significant economic investment required to obtain FDA clearance or approval and the difficulty of recouping investments in low-volume tests that treat rare conditions. Further, CLIA allows more rapid response and improvements to tests than do the time-consuming FDA approval and/or clearance processes. Given the speed of medical developments and patients’ time-sensitive needs for the most up-to-date treatments, the flexibility under CLIA for laboratories to incorporate these developments into LDTs provides significant benefits to patients who could be harmed by being forced to wait for a new or modified test to be cleared or approved by FDA.

Moreover, CLIA was tailored specifically to the regulation of clinical laboratory testing, a *service*, unlike the FDA regulatory scheme, which was designed to regulate commercially distributed *products*. The Petition’s assertion that LDTs should be regulated in the same manner

⁶⁷ FDA, *Critical Path Opportunities Report* (Mar. 2006), “Message from the Acting Commissioner,” [available at http://www.fda.gov/oc/initiatives/criticalpath/reports/opp_report.pdf](http://www.fda.gov/oc/initiatives/criticalpath/reports/opp_report.pdf).

⁶⁸ FDA, *Challenge*, at ii.

⁶⁹ *Id.* at i, iii.

as test kits merely because they are functionally similar fails to recognize the critical significance of this distinction—a distinction that Congress wisely recognized. This distinction between the testing services provided by clinical laboratories and the products marketed and sold by device manufacturers is not an arbitrary one but, rather, is one that recognizes important differences between these two situations. Different regulatory paradigms for services and products make sense for a number of reasons, including, in this instance, the different degrees of risk inherent in each approach. Assuming that an LDT and a test kit are functionally similar, a test kit is inherently riskier than an LDT at the moment of its creation because it is a product designed to be placed in a box and sold to an unknown entity for use, while the entity performing an LDT is always, by definition, the very laboratory that created it. If for no other reason, this inherent risk disparity merits a different and more rigorous level of scrutiny for test kits than for LDTs. Accordingly, it would be just as absurd to regulate LDTs under FDA’s regulatory scheme as if they were commercially distributed products as it would be to regulate device manufacturers under CLIA as if they were providing clinical laboratory services. Contrary to the Petition’s assertion, the existing differences in regulatory oversight for LDTs and test kits are not arbitrary, but entirely rational.

Moreover, there are irreconcilable conflicts between compliance requirements for “medical devices” regulated by FDA and for “clinical laboratory services” regulated by CLIA—both of which these laboratories would face under the Petition’s proposed policy. FDA requirements for medical device labeling and promotion would create impossible problems for compliance when LDTs are used in a clinical laboratory setting. Although the CLIA regulations clearly contemplate that clinical laboratories may modify FDA-cleared/approved tests (e.g., modify the analytical technique or use different reagents or steps) as long as the laboratory establishes the performance specifications of the modified test, it is not clear that a clinical laboratory that is considered a “medical device manufacturer” would be permitted to offer its test beyond the strict limitations of the labeling. Given the rapid advancement of this scientific area, CLIA offers flexibility to update and enhance tests (e.g., updating the laboratory test report to include recently published references that are relevant to the interpretation of the test). FDA rules would not permit such updates unless and until they were cleared for labeling through supplemental filings and clearances or approvals by FDA. These could take months to obtain and could be prohibitively costly, especially when considering the numerous incremental advances that are occurring with these tests on a regular basis.

Given that CLIA was designed specifically for the regulation of laboratory testing services and that it has demonstrated its success at this task over time, FDA regulation of LDTs, as the Petition requests, is unnecessary. The addition of FDA oversight in this area simply would place unnecessary burdens on clinical laboratories that are already highly regulated. Furthermore, FDA regulation of clinical laboratories as “medical device manufacturers” would raise a number of other issues, including:

- Identification of the particular regulated item among the test services offered by the laboratory;

- Duplication and inconsistency in quality systems requirements, including compliance with FDA’s prospective design control requirements for tests that already are developed under CLIA without such requirements;
- Duplication of inspections by FDA and CLIA;
- Compliance with labeling restrictions under FDA versus CLIA requirements to provide information and consultation to interpret test results for individual patients;
- Application of requirements for clearance/approval of enhancements and updates; and
- Acceptance, testing, and provision of reports for patients who fall outside FDA-cleared labeling that otherwise would be permissible under CLIA and under the practice of medicine.

The significance of these unresolved issues, combined with the fact that CLIA adequately addresses the oversight of LDTs while also fostering innovation and incorporation of medical advances into patient testing services, counsels that CLIA, as implemented by CMS, should continue to be the regulatory scheme applicable to LDTs.

VII. There is an Unresolved Legal Issue Surrounding FDA’s Authority to Regulate LDTs.

Contrary to the Petition’s statement that “FDA has ample legal authority to regulate LDTs,” there is an unresolved legal question about this.⁷⁰ The Petition states that FDA has authority because FDA has always said it has authority. This is tautological and insufficient to establish *bona fide* authority. Furthermore, ACLA believes that FDA does not have jurisdiction because LDTs neither constitute “medical devices” nor are they distributed commercially in interstate commerce—both requirements for FDA jurisdiction under the Federal Food, Drug, and Cosmetic Act (FFDCA).

First, the components of LDT processes are not marketed as kits or test systems, and they are not physically distributed or delivered outside the laboratory. Instead, laboratories provide written reports of the results to the ordering physicians after the laboratories have performed the tests within their laboratories. Thus, clinical laboratories that develop and perform LDTs are selling *services* to outside entities; they are not selling any identifiable *medical device*. We emphasize here the differences between the medical devices typically regulated by FDA and the services that are usually considered regulated under CLIA, but which the Petition would have FDA reach.

Moreover, even if LDT services were somehow considered “medical devices,” they still would not qualify for FDA regulation pursuant to FDA’s legal mandate under the FFDCA to regulate products intended for introduction into interstate commerce.⁷¹ Laboratories performing these tests are engaged in a process that does not involve any sale or distribution of a medical device to a third party. For these reasons, we believe FDA would be acting outside its legal authority if it sought to regulate LDTs.

⁷⁰ Genentech Citizen Petition, at 17.

⁷¹ See, e.g., U.S. v. Prigmore, 243 F.3d 1, 4 (1st Cir. 2001).

VIII. Conclusion

The Petition asserts that the existing, bifurcated approach to regulating LDTs and device manufacturer-developed *in vitro* diagnostic tests is unfair and arbitrary. In this response to the Petition, we have provided several examples of why the existing approach is both clinically appropriate and rooted in a rational statutory design. We also have identified a number of factual errors and false conclusions in the Petition. We would be happy to provide additional information or to discuss our views further with FDA if that would be useful. Thank you for your consideration.

Sincerely,

Alan Mertz, President