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September 15, 2010

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville MD 20852

RE: Docket No. FDA-2010-N-0274 – Oversight of Laboratory Developed Tests; Public Meeting; Request for Comments

EXECUTIVE SUMMARY

1. Clinical laboratories are providers of testing services; not medical device manufacturers, a fact that necessitates flexibility and innovative thinking on FDA's part in regulating LDTs. (See page 3 - 4)
2. Regulation of clinical laboratory developed tests (LDTs) should not vary based on the setting in which they are performed. LDTs performed by independent clinical laboratories are no more (or less) "commercial" than LDTs performed by hospitals, academic medical centers, or small labs. (See pages 5 - 6)
3. FDA's regulatory framework should be applied to LDTs with greater flexibility than is necessary for *in-vitro* diagnostic kits because LDTs are services whereas IVDs are sold as commercial products. (See page 6)
4. FDA should utilize existing Clinical Laboratory Improvement Amendments (CLIA) oversight and processes, including deemed accrediting agencies, to avoid duplicative or redundant governmental regulation. This should specifically be applied to site inspections and quality system regulations. (See pages 6 - 7)
5. Requiring clearance or approval of LDTs would set up an instant backlog for reviewers as well as a multi-fold increase in FDA's workload going forward, raising questions related to FDA's limited resources. Third party evaluators, if used, must be independent and without any conflict of interest or competitor bias. (See page 5)
6. FDA should "grandfather" the vast majority of well-accepted and well-understood tests already in clinical use to avoid disruption in patient care. (See pages 4 - 5)
7. Risk-based categories developed by FDA should be informed by additional stakeholder input. FDA should schedule a series of meetings with experts and stakeholders to explore

the granular details necessary for a fair and equitable risk characterization approach and to determine the level of evidence required for each category. (See page 6)

8. FDA should carefully consider which modifications to LDTs will require approval, clearance, or notification and how this can be done with minimal disruption in order to protect patient access to innovative improvements in testing. (See page 8)
9. FDA should consider other alternatives to premarket review, including labeling or disclosures. (See page 8)
10. FDA must allow for a transition period to any new regulations comparable to what was allowed when IVDs transitioned to QSR. The first year of any new regulatory scheme should be educational rather than enforcement driven. (See page 9)
11. Moving forward, FDA should use Notice and Comment Rulemaking procedures, which provide greater transparency than the FDA's Guidance approach. (See page 9)

ACLA SUPPLEMENTAL COMMENTS ON OVERSIGHT OF LABORATORY DEVELOPED TESTS

Dear Sir or Madam:

The American Clinical Laboratory Association (“ACLA”) is pleased to provide comments to the Food and Drug Administration (“FDA”) on issues related to the oversight of Laboratory Developed Tests (“LDTs”), which was the subject of FDA’s public meeting held on July 19 and 20, 2010. 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. All ACLA members produce and perform LDTs, and thus will be directly affected by any change that FDA makes related to the oversight of these tests.

We appreciate FDA’s solicitation of stakeholder input as it considers how to proceed regarding the regulation of LDTs. ACLA was pleased to be invited to participate in the public meeting held in July, and to provide comments. In these written comments, ACLA wishes to highlight certain key issues that we believe will require further discussion and analysis as FDA moves forward. As everyone acknowledged at the July meeting, the issues discussed herein present very difficult and complex questions. Therefore, ACLA hopes to have additional opportunities to provide input in greater detail as FDA moves forward. We have requested a series of interactive meetings with FDA to discuss regulation of LDTs and hope that these meetings will allow for a productive two way dialogue on the specifics before any regulatory approach is proposed.

1. Introduction

Independent and hospital based clinical laboratories, physician pathology practices, and university medical centers all develop and validate tests in their own laboratories for physician-directed patient care. Examples of LDTs range from commonly used tests, such as Pap smears, manual blood cell counts, erythrocyte sedimentation rates, microbiology cultures and susceptibility tests, among many others, to new advanced molecular diagnostics, which derive from the mapping of the human genome and which will be central to fulfilling the promise of personalized medicine. Thus, in discussing LDTs, it is important to acknowledge the number and scope of the tests, and the part they play in virtually all clinical laboratory testing.

Given the widespread use of LDTs, and their application to new types of testing being developed, ACLA believes it is vital that FDA proceed cautiously and thoughtfully. We were pleased at the July meeting that FDA recognized the importance of not inhibiting innovation, especially at the time when these tests present such potential. In our comments below, we have tried to highlight some of the areas where we believe FDA must be particularly careful in order to mitigate any potential disruption that could work to the detriment of patients who will be benefited by innovative new testing.

Our overarching concern is one that was also expressed at the July meeting: laboratories are providers of testing services; they are not medical device manufacturers. Thus, we have great concern about the FDA imposing its regulatory scheme, which was designed to regulate medical device manufacturers, onto a completely different industry (clinical laboratories), for which that regulatory approach was not only *not* intended, but which is also already subject to a different regulatory scheme specifically tailored to it (the Clinical Laboratory Improvement Amendments of 1988 (“CLIA”). Regulation of LDTs by FDA should be based on an understanding of the differences between laboratory services and the products used by clinical laboratories to perform tests. Clinical laboratories are not “traditional” medical device manufacturers, a fact that necessitates flexibility and innovative thinking on FDA’s part.

As discussed in greater detail below, we believe there are certain key issues that the FDA must resolve as it moves forward with this initiative. These include the following:

- What is the best way for FDA to manage the significant task of LDT regulation?
- Should all LDTs be subject to the system that the FDA develops?
- How should FDA’s authority and that of CLIA be reconciled?
- In a system based on risk, how will issues of risk be stratified?
- What type of evidence will be required for those tests that will go through FDA approval or clearance?
- Which types of test modifications will require FDA oversight?
- What unique issues are created with regard to labeling and disclaimers?
- What is the timing of these developments?
- What, if any, role is there for the NIH’s proposed genetic test registry?
- What is the best process for identifying all of the issues and moving forward?

2. Options for Managing the Task

The FDA has recently estimated that there are between 2,500 and 5,000 different LDTs available to patients today. ACLA members across the country perform most of these LDTs and we believe we could provide FDA with substantive input with regard to this type of testing. Today, FDA approves a single premarket review application for a test kit which then is utilized by thousands of laboratories throughout the country. The question is how FDA will approach the regulation of the tests performed at the thousands of clinical laboratories each developing hundreds of the same or similar LDTs. If the FDA were to exercise oversight over all of these tests, it would be a substantial undertaking, as the agency is well aware.¹ ACLA believes that managing this sizable task at the outset without causing a disruption in patient access will require “grandfathering” of most currently-available tests.

Requiring clearance or approval of the thousands of tests currently in use would likely set up an instant backlog for the reviewers. ACLA believes that the vast majority of LDTs currently in use present little or no risk to the patient because they are well-established and widely used. We believe that FDA should consider exempting all existing tests from pre-market review or continuing to

¹ Even these numbers underestimate the scope of FDA’s potential task. Because each laboratory develops its own LDT, under some conceivable regulatory schemes, the FDA would have to oversee each entity’s particular test, even if such tests are all for the same use. Thus, for example, FDA would have to separately review each laboratory’s Cystic Fibrosis test, notwithstanding the fact that they may all be similar and have the same intended use.

exercise its “enforcement discretion” with regard to such tests. This type of grandfathering seems crucial to establishing a workable approach to the regulation of LDTs and to preserving FDA’s limited resources. It is also essential to avoiding disruptions in patient care.

FDA may wish to consider various criteria for such a grandfathering. It may wish to design a grandfathering strategy based on the date on which a test was first offered to patients, or focus on a post-market surveillance approach for tests already on the market. Another option, at least for some tests, may be using New York’s premarket review of tests as a point of reference. New York currently reviews most new LDTs in the area of molecular diagnostics. While we are not suggesting that premarket review is necessary for the majority of LDTs or that the New York model should necessarily be adopted by the FDA (given the lengthy delays experienced by some laboratories for some LDTs), FDA could consider “grandfathering” tests which have previously been approved by New York State.

We also note that FDA has stated that it could consider using third party reviewers or validators to help ease the burden of LDT oversight, an approach that could be promising. If FDA takes this approach, however, it is important to ensure that any third party would be independent and would not have a conflict of interest in reviewing what could be proprietary and competitively sensitive information.

3. Scope of FDA Oversight

ACLA strongly believes that whatever risk based system is developed should apply equally to all laboratories utilizing specific types of LDTs. Put another way, laboratory tests should not be classified based on the setting in which they are performed. If FDA elects to involve itself with the oversight of LDTs, its oversight should extend equally to tests performed at hospital laboratories, in physician pathology practices, in universities or academic settings, and by independent clinical laboratories. The innovation that occurs in all of these settings, a key part of offering LDTs, must be encouraged, not discouraged, by the agency. FDA has frequently stated that one reason it is considering expanding its involvement in this area is because of what it perceives to be an uneven playing field between manufacturers and laboratories. Given that concern, it would be unreasonable in the extreme to create a different, but equally uneven, playing field that distinguished between independent laboratories using LDTs and other types of facilities creating and using these same LDTs.

During the July meetings, FDA referred to “commercial tests” as distinct from hospital-based tests. It apparently based this distinction on the perceived relationship between the patient, pathologist, and clinician in the hospital setting as opposed to the non-hospital setting. This suggests that FDA believes that physicians have a greater opportunity to interact with the pathologist or other laboratory personnel in the hospital setting than in other settings. This is simply not true. CLIA requires all clinical laboratories, whether located within hospitals or otherwise, to have a clinical consultant who is available to consult with outside physicians about the testing performed and the results. 42 C.F.R. § 493.1457. The same is true for tests performed in academic settings. All laboratories providing clinical testing services, including LDTs, have resources in place to support a relationship with the health care provider ordering the service and the patients they serve in understanding the testing offered and results.

Regulation of LDTs should therefore be standardized across these settings. LDTs performed by independent laboratories are no more (or less) “commercial” than LDTs performed by hospitals, academic medical centers, or small laboratories. In sum, regardless of the setting in which a test is offered (clinical laboratory versus hospital laboratory or direct-to-consumer (DTC) versus physician-ordered), claims for use should be regulated in the same manner.

It remains important to note, however, that while all LDTs should be regulated in the same manner regardless of setting, it is entirely appropriate and consistent with this position for FDA to apply its regulatory framework in different ways to LDTs and commercially distributed *in vitro* diagnostic test kits (IVDs). This is because the key distinction between LDTs and IVDs is not based on the settings in which they are used or performed (or even on the settings in which they are developed), but rather on the fact that LDTs are services developed and used within a single entity whereas IVDs are products sold commercially to numerous entities of varied size and experience. For that reason, a more flexible application of FDA’s regulatory framework to LDTs than to IVDs is appropriate, even when there is no distinction in classification based on setting.

4. Ensuring Non-Duplicative Oversight

The overarching threshold challenge for FDA as it considers regulation of LDTs is to identify the gaps in the current oversight scheme. As has been frequently noted, laboratories are already subject to oversight under CLIA, and there is a great deal of potential overlap between FDA and CLIA requirements. If gaps in oversight are identified, however, then all stakeholders should be consulted to determine what steps are necessary to close the gaps, taking into account the principles of least burdensome regulation, practice of medicine, and avoiding disruptions to patient care.

To the extent possible, we urge FDA to utilize CLIA to ensure least burdensome oversight of LDTs. Because laboratories are already highly regulated under CLIA, our understanding is that the FDA’s focus is laboratory tests themselves. While the approaches FDA is considering for regulating LDTs should necessitate close collaboration between FDA and CMS, we believe special care must be taken to avoid duplicative or redundant governmental actions. For example, we are especially concerned about the potential for duplicative inspections by both CLIA (and its accrediting organizations) and FDA. Since CLIA certification and inspection is well-established, thorough, and effective, we urge FDA to utilize that structure, rather than layering on an additional level of inspections.

CMS, along with its accrediting organizations, is best suited to continue providing quality assurance of laboratory practices under its CLIA authority. If FDA believes that other areas need to be included, such as design controls, then we suggest that FDA work with CMS to have such information added to the inspection process. FDA should also be sensitive to overlapping regulatory oversight to avoid redundant – or conflicting – FDA quality system requirements.

5. Risk Characterization

In its recent statements, the FDA has emphasized the importance of moving to a risk-based approach. However, the key to any such approach will be the criteria used to stratify risk and how they are applied. All presenters at the July meeting, and FDA, recognized how complex such an

exercise will be. As FDA moves forward, it should balance both parts of its mission – to protect but also to promote public health. This balance can only be achieved if risk characterization includes benefit-risk assessments and does not delay access to innovative new services.

The intended use of a test as described by the applicant and the medical claims made by a laboratory offering a test should be the major determinants when assessing a test's risk. When fully explored, these elements allow for the consideration of benefits as balanced against risk. In determining where tests lie on the risk-benefit spectrum, FDA should take into account a number of factors:

- Are the tests' uses transparent and well-understood?
- Are the tests used for rare disorders?
- Is there no other test available?
- Are the tests for single or even multiple analytes where there is a clear and well-accepted link to clinical outcomes?

In the case of tests used for rare diseases, for example, a higher level of risk or less validation data may be tolerable because there may be no other viable alternative. In addition, tests that are not the sole determinant of diagnosis or treatment for a serious or life threatening condition present lower risk than those that are. As an example, the Pap smear is a valuable test for the serious life threatening condition of cervical cancer, but it is not the sole determinant of diagnosis or treatment for cervical cancer – it is used in conjunction with other diagnostic tests such as HPV, colposcopy and tissue biopsy. In another example, trait determination or ancestry tests present less risk than results on which medical decisions will be based.

While “intended use” should certainly be considered as FDA decides how to prioritize its limited resources, even this criterion presents difficult issues. For example, while FDA should consider claims made by the laboratory, FDA should avoid characterization based on other potential ways that health care providers may decide to use a test, as such uses relate to the practice of medicine. Similarly, the line between predisposition testing (one intended use) and diagnostic testing (another intended use) is often blurred. Therefore, even intended use may not always be a clear determinant of risk classification. However, regardless of the setting in which a test is offered, the same claims for use should be regulated in the same manner, provided that services are not treated as if they were products.

It is also critical for the FDA to evaluate the risk of a test in the context of the existing standard of care. To evaluate risk solely on the basis of potential harm from an erroneous result is only to look at one slice of the risk pie, and completely ignores the risk of harm that may be presented when regulation prevents or delays availability of a test where none currently exists or where a less safe and effective alternative exists. To assess risk accurately, FDA must weigh the patient harm that could result from a false result against the patient harm that could result from no result at all. FDA should be careful to avoid unintended consequences in situations where applying rigorous requirements for approval would prevent innovative and promising tests from being made available to patients. This is particularly important in the case of tests for rare diseases or conditions.

Finally, ACLA believes that risk-based categories developed by FDA should be informed by substantial additional input from the industry most affected by the regulatory changes. ACLA will continue to work with the agency to develop appropriate criteria for risk-based categorization of tests and to determine the appropriate evidence requirements linked to each risk-based category. However, given the complexity of the issues related to risk characterization, we think it is especially important for FDA to consider a series of dedicated meetings with experts and stakeholders who can examine at a very granular level the difficult questions that must be faced in this process. Collaboration and discussion will be especially important as FDA and the industry wrestle with determining whether and how to apply FDA's existing classification system (or a variation of that system) to LDTs. We appreciate that FDA has recognized the difficulty of these issues, and ACLA looks forward to discussing them further at upcoming meetings with the FDA.

6. Evidence Requirements

The other major issue that will have to be decided is what levels of evidence will be required for those LDTs that will be subject to FDA approval or clearance. For any new product, various types of evidence will often be available. While randomized clinical trials are often considered the "gold standard" for certain high risk drugs or devices, they will often be impractical for diagnostic tests. To avoid an adverse effect on patient care and innovation, FDA should recognize alternative evidentiary sources for LDTs such as observational studies, studies using archived specimens, and academic reviews in published literature. If evidence requirements are too stringent, they will stop the very innovations based on discoveries about the human genome that has been so beneficial to patients over the past decade.

The level of evidence required will also necessitate an evaluation of what other types of information are available. For example, it may be reasonable to require a lower level of evidence when no other diagnostic test is available. Allowing use of a test that is less-than perfect may be better than having no test at all. So long as adequate disclosures are made about the uses of such a test, physicians who want to order the test for their patients will often value having such an option available.

7. Modifications to Cleared/Approved LDTs

Another important area for FDA to consider is how any new oversight process would deal with the frequent modifications that laboratories typically make to their tests. Indeed, numerous commenters at the July meeting highlighted the ability of laboratories to quickly adjust to new information or new discoveries as one of the greatest advantages of LDTs. Currently, laboratories are able to continuously make improvements to LDTs, so long as they are validated in accordance with the CLIA regulations. Such changes might include adjusting the assay to allow for increased test volumes, shifting sequence position of primers or probes when new variants are recognized, validating additional sample types or collection devices when appropriate, or improving reagent concentration. Resubmission to FDA for every modification of an assay could delay innovation or be a disincentive for assay improvement and thus slow the promise of personalized medicine. Patients should continue to have timely access to improvements and innovations offered by modifications in molecular diagnostic testing and other LDTs. We urge FDA to carefully consider which modifications to LDTs will require approval, clearance, or notification and how this can be done with the minimal disruption.

8. Labeling and Disclaimers

In some instances, it may be useful for FDA to consider labeling or disclosures as an alternative to certain forms of approval or clearance. For example, where a test is developed for a rare disease or not subject to a major validation study because it is developed in response to an emerging health care need, requiring a statement or disclosure on the label may be preferable to not approving or clearing the test due to insufficient evidence. In addition, if an LDT is only going to be used within a single laboratory – as is typical for LDTs – then such a limitation could be included in the labeling. This limitation could also permit lowering the other regulatory requirements applicable to the test. That is, if the test is not going to be sold to other laboratories and will only be used in house, then it may not be necessary to include all of the various types of controls that would be included for a test kit that will be sold to numerous other entities. We hope that FDA would be judicious in requiring such disclaimers, as disclaimers should be informative, but not used to restrict access to tests.

We also note that, because LDTs are services rather than products, there is no physical packaging on which to affix a label. Rather, FDA should consider that product labeling will be limited to statements made on test reports and in the laboratory's directory of services.

9. Transition Period

As FDA recognizes, the changes being considered are significant for laboratories, physicians, and for the FDA itself. Even if FDA makes fairly limited changes, they will require extensive time and education before they can be implemented. Therefore, we believe that FDA must allow a lengthy transition period comparable to that which FDA has permitted in the case of other regulatory changes, such as the 30 month period that was allowed when IVDs transitioned to QSRs. The first year of any new regulatory regime should be educational, rather than enforcement-driven. ACLA also urges FDA to consider grandfathering those tests – likely the majority of LDTs – which are commonly used and generally accepted as the standard of care.

ACLA looks forward to continuing to work constructively with FDA toward a regulatory approach that will allow physicians and their patients to continue to benefit from the numerous vital contributions to improved health care provided by laboratories through LDTs.

10. Genetic Test Registry

At the meeting in July, there was a great deal of discussion concerning the NIH's Genetic Test Registry. ACLA believes that the registry could be an important tool for providing all interested parties with valuable information about what tests are available. We have already provided input to NIH in response to their request for information and look forward to continuing to work with them on their plans.

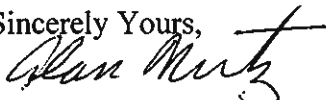
11. Procedure for Further Guidance

At the July meeting, FDA officials indicated that they did not believe it was necessary for the agency to proceed through formal notice and comment rulemaking, but rather that they were

likely to use the FDA's Guidance approach. During the formulation of the IVDMA Guidance, ACLA raised concerns regarding FDA's decision to approach regulation of IVDMA through Guidance rather than through more formal Notice and Comment Rulemaking. Generally, we believe the rulemaking process provides greater transparency by ensuring that the agency considers and responds to comments and concerns raised by stakeholders. While FDA usually accepts comments on Guidance documents, that process does not usually include the same level of transparency. For example, the agency is not required to formally respond to the comments that are received and the agency is not required to base its decision on the whole record. Further, the FDA has proceeded through more formal rulemaking in related areas in the past, for example, in the formulation of the analyte specific reagent (ASR) rule, which was the starting point for many of the issues that are currently under consideration. Given the significant change in policy that is represented by the FDA's proposed action here, ACLA believes that notice and comment rulemaking is not only preferable, but may even be legally required.²

Nonetheless, regardless of whether FDA proceeds through rulemaking or guidance, it is most important to have a transparent process that permits robust discussion and industry input. This type of process will be essential to resolving the complex issues involved. We understand that FDA is planning to proceed with other meetings to further explore the issues that may be created by this new regulatory initiative. ACLA looks forward to participating in such meetings with FDA and with others in the clinical laboratory community as discussion continues on these very important questions.

Thank you for the opportunity to comment on these matters. If you have questions or need any further information, do not hesitate to contact us.

Sincerely Yours,

Alan Mertz, President

² In addition, there are unresolved issues related to FDA's authority in this area that would be best explored in the context of the rulemaking process.