Biotechnology Industry Organization

February 2, 2015

VIA electronic delivery
Margaret Hamburg
Commissioner
United States Food and Drug Administration
Division of Dockets Management (HFA-305)
5630 Fishers Lane Rm 3128

Dear Commissioner Hamburg:

The Biotechnology Industry Organization (BIO) appreciates the opportunity to submit comments on two draft guidance documents released on October 3, 2014, entitled *Framework for Regulatory Oversight of Laboratory Developed Tests* (the "Framework Guidance") and *FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)* (the "Notification Guidance) (collectively the "LDT Guidances"). BIO represents approximately 1,000 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnologies, thereby expanding the boundaries of science to benefit society by providing better healthcare, enhanced agriculture, and a cleaner and safer environment. Specifically, a number of BIO companies develop, market, or are impacted by molecular diagnostic technologies for a variety of research, investigational, and clinical uses. BIO's membership includes companies that develop diagnostic kits, sole-source innovative laboratories, therapeutics, and research tools.

BIO supports patient access to high-quality, innovative diagnostic tests for actionable biomarkers (*i.e.*, tests that impact clinical decision-making). Access to high-quality diagnostic testing is the cornerstone of personalized

1201 Maryland Avenue SW
Suite 900
Washington DC 20024

202.962.9200
202.488.6301
bio.org

medicine, ensuring the right patients are treated with the right drug, at the right time.

In these comments, BIO provides recommendations to the Food & Drug Administration ("FDA" or "the Agency") regarding how the Agency might improve some of the concepts and provisions in the LDT Guidances to ensure continued innovation in the development of molecular diagnostics and the avoidance of disruption to patient access for these important products. We appreciate the opportunity to work with FDA to assist the Agency in developing the least burdensome and most efficient approach to regulating laboratory developed tests ("LDTs"). BIO also commends FDA for incorporating stakeholder input the Agency received in previous requests for comments, such as at the 2010 public workshop on the regulation of LDTs. BIO urges FDA to continue to incorporate stakeholder feedback on the LDT Guidances, and consider practical approaches that maximize the ability for LDT developers to comply to ensure continued availability of these important products to the care of patients.

We note that the opinions among BIO's membership vary regarding whether FDA has the authority to regulate LDTs under the Federal Food, Drug, and Cosmetic Act. Even among those that do, there is disagreement regarding whether such regulation is in the best interest of the medical community, including patients who might benefit from these tests. Similarly, there is a difference in opinion regarding whether FDA should proceed with these regulatory changes in the context of rule-making or through the guidance document process. Accordingly, BIO does not take a position as an organization on either of these issues. Further, nothing in these comments is intended to impact adversely in any way the ability of individual BIO members, alone or in

combination, to pursue separate comments, litigation or other remedies with respect to FDA's proposal to regulate LDTs.

I. Delayed Release of the Risk Classification and Other Guidance Documents Results in a Lack of Clarity That Could Negatively Impact Investment and Patient Access for Molecular Diagnostics

BIO appreciates that FDA proposes a risk-based, phased-in approach over a nine-year period to regulate LDTs under the Federal Food, Drug, & Cosmetic Act. This flexibility, practicality, and allowance for time is critical to ensure that LDT developers are able to comply with the LDT Guidances. In addition to providing adequate notice to those currently marketing these products to comply, FDA should ensure that there is adequate clarity and specificity in the proposed timeline of regulation, such that investment continues to promote innovation in the development of molecular diagnostics.

Under the Framework Guidance, the requirement and timing to file a pre-market submission for a LDT depends on the classification of risk by FDA. The Framework Guidance provides some delineating information regarding tests that will fall into the highest risk categories,[1] and thus require filing a pre-market application 12 months after finalization of the LDT Guidances. The Framework Guidance provides further that remaining high-risk devices will be phased in over a 4-year period. LDTs falling into the medium and low risk categories would either receive continued enforcement discretion or have to come into compliance over 9 years following finalization of the LDT Guidances.

---

[1] The Framework Guidance defines these products as "LDTs with the same intended use as a cleared or approved companion diagnostic, LDTs with the same intended use as a FDA-approved Class III medical device, and certain LDTs for determining the safety or efficacy of blood or blood products." Framework Guidance at 24.

In the Framework Guidance, FDA notes that it will use the existing risk classification system under 21 Code of Federal Regulations Part 860 to classify LDTs as Class III, II, or I medical devices.[2] FDA states in the Framework Guidance that it will publish priority lists placing LDTs into the various risk categories for remaining Class III LDTs, and Class II LDTs at 24 months and 48 months, respectively. However, for the LDTs that will fall into the remaining high-risk, moderate-risk and low-risk categories, no guidance is provided by FDA to enable LDT developers to prospectively identify the appropriate classification for products developed over the course of the implementation timeline under the LDT Guidances. FDA states in the Framework Guidance that there is a need for "additional clarity" regarding what FDA "considers generally to be Class I, II or III."[3] Accordingly, FDA intends to publish draft guidance addressing this issue 18 months following finalization of the LDT Guidances, with finalization of that guidance document 6 months later.

Under this proposal, LDT developers that are in the process of developing products and building the necessary evidence base to comply with FDA marketing requirements are left without adequate clarity regarding where along the regulatory compliance timeline their products will fall. BIO agrees with FDA that additional clarity is needed to allow LDT developers to predict with reasonable certainty which category their product will fall into, and thus know the timing and type of pre-market submission that will be required. Accordingly, FDA should publish and finalize this LDT classification guidance document as soon as possible. FDA should make every effort to publish this guidance

[2] Promulgated under authority of Section 513(a)(1) of the Federal Food, Drug, & Cosmetic Act.
[3] Framework Guidance at 12.

document sooner than the proposal to publish it 18-24 months after finalization of the guidance document.

Failure to prospectively clarify what risk category a particular LDT will fall into leaves LDT developers without sufficient information to plan to build the evidence necessary to support the pre-market submissions required under the LDT Guidances. The 12-24 month windows provided under the guidance for compliance following publication of the respective priority lists may not be adequate to allow time for the conduct of clinical studies, and may not allow enough time for LDT developers to prospectively plan. This lack of clarity could threaten continued investment in molecular diagnostics, and create inefficiencies that could result in decreased patient access to these products.

Furthermore, BIO is concerned that FDA is moving forward with this guidance despite the existence of key, known questions relating to specific types of LDTs. Specifically, BIO urges the Agency to publish, as soon as possible, guidance documents relating to the regulation of next generation sequencing, as many of the issues raised in this guidance are difficult to apply for high-throughput, multi-plex platforms. BIO also understands that FDA plans to publish a companion diagnostic device specific guidance document that will address "me too" types of products, and also a guidance document addressing LDT compliance with quality systems regulation ("QSR"). (see discussion below in Section II)

II. FDA Should Provide Detailed Guidance on How LDT Developers Can Comply with the Quality Systems Regulation in a Manner Consistent with CLIA and In the Context of the Provision of Laboratory Services

BIO supports FDA's application of a system to ensure that the processes by which LDTs are developed lead to high-quality, consistent, and accurate results for patient care. However, BIO is concerned regarding potential for conflict and/or confusion between the regulatory requirements that laboratories are subject to under the Clinical Laboratory Improvement Amendments of 1988 ("CLIA") and new requirements that would be imposed under the LDT Guidances, particularly as it relates to compliance with the QSR.[4] As FDA looks to apply QSR to LDTs, the Agency must consider the differences between developing an assay for release and use, versus the processing of a patient sample in a laboratory. BIO is concerned that the rapid timeline for compliance and a lack of guidance specific to the clinical laboratory setting may prove challenging for compliance.

FDA should harmonize its requirements with the requirements under CLIA, and ensure that any new regulatory requirements are complementary and not in conflict with CLIA.[5] As one example, whereas manufacturers of traditional IVDs manufacture a kit in batches to be released in compliance with QSR, laboratories typically do not engage in such manufacturing activities, but may prepare and consume reagents in the context of processing a patient sample. In such cases, where laboratories are not performing manufacturing activities, the concepts of batch release and expiration of product will be different. The

---

[4] Codified at 21 C.F.R Part 820.
[5] Compare 21 C.F.R Part 82'0 and 21 C.F.R. Part 493.

processing of a patient sample will be performed with a collection of reagents, which may expire at different times.

As another example, due to the differences in how diagnostic kits and LDTs are distributed/performed, there should be allowances made for differences in how labeling requirements are met. For example, the Federal Food, Drug, & Cosmetic Act authorizes the use of electronic labeling in certain circumstances,[6] which should enable laboratories to use their online directory of services as a source for labeling.

BIO encourages FDA to engage the laboratory community to identify other areas of potential conflict and/or confusion. BIO urges FDA to publish a joint draft guidance document with the Centers for Medicare & Medicaid Services ("CMS"), in conjunction with a public process for comment consideration from all stakeholders. FDA should consider a joint public workshop in conjunction with CMS to analyze and compare the QSR and CLIA regulations, focusing on existing gaps and how laboratories could go about fulfilling the gaps. In the event that FDA does not publish such a guidance document in parallel with the LDT Guidances, FDA should provide general guidance on the case by case reconciliation for individual LDTs that would occur upon inspection of laboratories, as mentioned by the Agency in the webinar that it held on October 23, 2014.

To assess the QSR for areas of potential confusion as applied to the laboratory setting, FDA should evaluate the following areas for confusion and any unnecessary burden under the QSR regulations for LDTs in the following areas: quality system requirements, document controls, purchasing controls,

---

[6] See Section 502(f)(2) of the Federal Food, Drug, & Cosmetic Act.

production and process controls, acceptance activities, nonconforming products, corrective and preventative actions, and records. Further guidance on these issues is critical to ensure that laboratories, attempting in good faith to comply with QSR, are able to meet these requirements.

III. FDA Should Consider Expanding the Threshold for the Rare Disease Exception under the Framework Guidance, and Extend Enforcement Discretion to All *In Vitro* Diagnostic Devices

The Framework Guidance proposes an exception for partial enforcement discretion for LDTs where "the number of persons who may be tested with the device is fewer than 4,000 a year."[7] In the Federal Register notice announcing publication of the Framework Guidance, FDA asks for comments concerning the appropriateness of the 4,000 testable patients standard, and whether FDA should extend enforcement discretion to *in vitro* diagnostic devices (IVDs) that do not meet FDA's definition of a LDT – that is, a test that is designed, manufactured and used within a single laboratory.[8] BIO believes that FDA should consider a higher threshold for enforcement discretion for molecular diagnostic products intended to diagnose conditions for rare diseases, and that this enforcement discretion should extend to molecular diagnostics manufactured as a kit and distributed to multiple laboratories (herein referred to as "traditional *in vitro* diagnostic devices"). Specifically, BIO believes that FDA should increase the rare disease exception threshold to a population of 200,000 per year, and apply this enforcement discretion equally to traditional *in vitro* diagnostic devices.

---

[7] Framework Guidance at 20.
[8] 79 Federal Register 59778 (October 3, 2014).

In the rare disease/orphan products area, FDA should strive to encourage the development of tests to serve these smaller patient populations. In the context of orphan drugs, incentives for development are triggered in patient populations where the prevalence of disease is fewer than 200,000 patients in the United States.[9] In many of these cases, the drug may be administered multiple times or over the course of years for treatment. In contrast, molecular diagnostics frequently are administered only once to achieve the diagnosis or guide therapy. However, the number of patients used for the standard for LDTs under the guidance is far less than the comparable standard for orphan drugs (*i.e.*, 4,000 vs. 200,000 persons in the United States with the disease or condition). FDA should use its enforcement discretion to decrease the burden on LDT and *in vitro* diagnostic device developers by normalizing these two thresholds.

While relying upon the definition of a Humanitarian Use Device, codified at 21 C.F.R. § 813(n), FDA's proposal to exercise enforcement discretion for LDTs that meet this definition creates an unfair disadvantage to traditional *in vitro* diagnostic device manufacturers. A traditional *in vitro* diagnostic device is required under the HUD statutory and regulatory provisions to submit an HDE, which is similar in both form and content to a PMA, but is exempt from the effectiveness requirements of a PMA. BIO is concerned that bifurcation in regulation will create a disincentive for traditional *in vitro* diagnostic device manufacturers to develop devices for rare diseases where research and development costs could exceed market returns. Accordingly, we recommend FDA expand the threshold for the rare disease exception to apply to diagnostic kit manufacturers as well.

---

[9] 21 U.S.C. §360(bb).

IV. FDA Should Ensure that the Unmet Need Exception Encourages the Development of All Innovative *In Vitro* Diagnostic Devices

In the Framework Guidance, FDA creates an exception for LDTs where no FDA cleared or approved IVD is available for that specific intended use. BIO appreciates FDA's intention to minimize disruption of testing by LDTs currently on the market in areas of unmet need. However, BIO is concerned that there is a lack of clarity regarding whether this exemption applies to LDTs on the market at the time of publication of the relevant priority list, or if it applies to LDTs entering the market after the lists are published. If the latter applies, BIO is concerned that this would create a disincentive for traditional *in vitro* diagnostic devices to go through the FDA process for similarly situated new tests, which are required to rely upon FDA's early/expanded access programs (emergency use, compassionate use, treatment use and continued access). This disincentive could inhibit private sector investment towards the development of new molecular diagnostics. FDA should clarify the application of this standard in future drafts of the Framework Guidance, and ensure that the exception does not create inequities between the developers of LDTs and traditional *in vitro* diagnostic devices.

Moreover, consistent with the rare disease exception above, FDA should also exercise enforcement discretion for diagnostic tests (whether LDT or traditional *in vitro* diagnostic devices) that are innovative and adopted by a relatively small number of patients per year during the test's first few years after being launched. Section 5 of the Framework Guidance refers to the Humanitarian Device Exemption, and "provides an abbreviated regulatory pathway as an incentive for the development of devices for use in diagnosis of rare diseases or conditions." Developers of genuinely novel or innovative tests—

of which there are historically few in the diagnostics industry—require the same incentives as those who develop tests to rare diseases as they face comparable financial risks and uncertainties.

V. The Definition of a LDT in the Framework Guidance Should Exclude Investigational Companion Diagnostic Devices

LDT biomarker tests (sometimes referred to as investigational companion diagnostic tests) are often used to make patient management decisions during an early-phase therapeutic clinical trial. The regulatory pathway for these LDT biomarker tests in an investigational setting, especially during early stage development, is vague, constantly evolving, costly, and not fully aligned with the drug approval process. Regulatory uncertainties unnecessarily complicate and prolong efforts to make companion diagnostics and their associated precision medicines available to clinicians and patients.

Investigational LDT biomarker tests appear to be subject to FDA Investigational Device Exemption (IDE) regulations. However, the appropriate level of documentation required for compliance with the FDA IDE regulations in this context is unclear. In current practice, FDA applies the IDE regulatory requirements in a non-standardized, case-by-case manner. Therefore, we request that FDA extend enforcement discretion to investigational LDT and IVD biomarker tests used in early stage non-pivotal (i.e., Phase 1/2) clinical investigations. BIO agrees with FDA that where there are LDTs/IVDs that have been marketed without prior regulatory oversight but will be moved into pivotal clinical trial settings for a new intended use, these LDTs/IVDs should be subject to FDA IDE/IND requirements to ensure patient safety.

BIO recommends that FDA clarify in the Framework Guidance that the definition of LDT does not apply to these LDT biomarker tests when used in clinical investigations. FDA should clarify that the LDT definition under the Framework Guidance is not intended to encompass diagnostic tests used in phase one, phase two, or other early-phase clinical trials. FDA should exclude LDT biomarker tests used in early clinical research from the definition of LDT in the Framework Guidance, and should also clarify that traditional IVDs used in these early phase clinical settings would be subject to the same enforcement discretion.[10]

VI. FDA Should Consider Expanding the Definition of a Single Laboratory in the Framework Guidance to Laboratories with Multiple CLIA Certificates, Where under Common Ownership and Quality Systems

FDA should consider the breadth of the definition of an LDT and a single laboratory in the Framework Guidance, as it relates to the limitation of a single CLIA certificate.[11] BIO encourages FDA to consider whether it may be more appropriate to define a single laboratory to include laboratories with more than one CLIA certificate, if under common ownership with a common quality system (taking into account lab-specific items, such as identifying instrument model numbers).

---

[10] BIO recognizes that there may be cases where a test is currently being marketed and fits the profile of a traditional LDT, but then is also investigated as part of a clinical study with either the original single-site acting as the clinical laboratory, or the technology is transferred to multiple sites to support the protocol. If such a test has not previously undergone validation and proficiency testing at these new sites, then it may be reasonable to require it in order to ensure consistency of performance across all sites.

[11] See footnote 5 of the Framework Guidance.

VII. FDA Should Clarify the Parameters Regarding When an LDT Developer May Rely Upon Literature to Demonstrate Clinical Validity

BIO supports FDA's proposal to rely on literature where it is adequate to meet the requirements for marketing under the Federal Food, Drug, & Cosmetic Act. FDA states in the Framework Guidance that, "if appropriate," laboratories may use existing literature to support clinical validity of LDTs.[12] BIO believes that, to the extent prospectively possible, FDA should describe the particular circumstances where the Agency believes that reliance on clinical literature may be appropriate. In particular, FDA should articulate when and what types of concordance studies might be required to tie the evidence in the published literature with the marketed LDT. BIO notes that, despite the existence of mechanisms at FDA for "paper NDAs" and "paper PMAs", these regulatory vehicles have been used relatively infrequently. The reliance on clinical literature by the agency to support marketing should be consistent, regardless of whether the test is manufactured in a clinical laboratory or by a diagnostic kit manufacturer.

VIII. Reporting Under the Medical Device Reporting Regulations Should Be Limited to Device Malfunctions (*i.e.*, Failures in Analytical Validity)

BIO agrees with FDA that the collection of adverse event reporting is important for LDTs to ensure that safety signals are identified and may be properly addressed by the Agency. Although the LDT Guidances set forth the requirement for adverse event reporting, they do not adequately define what nexus must exist between the information received and the test result to trigger

---

[12] See The Framework Guidance at 13.

the requirement to report. The LDT Guidances are unclear whether the requirement to report is related to the analytical or clinical validity of the information.

FDA should clarify whether the requirement to report an "adverse event" is due solely to a device malfunction (*i.e.*, analytical validity), or is triggered by an adverse event relating to downstream treatment or management of the patient by the clinician. BIO believes that a requirement to report based on information received regarding events that occur after variable downstream treatment and management would be too difficult to establish a truly associated relationship. It is not practical, nor appropriate, to attempt to establish a sufficient nexus of causation to the LDT based on an adverse event due to a change in treatment or management (*e.g.*, altering the selection of a drug based on a totality of the clinical presentation, unless the cause is due to a malfunction of the expected operation of the device. Accordingly, BIO recommends that reportable adverse events should be limited to occurrences due to device malfunction – failures in analytical validity resulting in false positives, false negatives, or delayed clinical results. FDA should apply these reporting requirements to all IVDs, whether LDTs or traditional IVDs.

IX. BIO Supports Third Party Review for Moderate Risk LDTs and Urges FDA to Clarify the Standards for Review and the Process for Adjudicating Disagreements

Consistent with historical practice for Class 2 medical devices, FDA states in the Framework Guidance that it will use third party review for LDTs that fall into the moderate-risk category. BIO supports the use of third party review to ensure adequate resources to process pre-market submissions under the LDT Guidances.

Despite this support, BIO is concerned that the LDT Guidances do not adequately address how FDA will ensure that the third party reviewers adhere to and apply the same standards of review. This is particularly problematic where no device-specific guidance documents exist for the product to be reviewed, which will largely be the case for LDTs reviewed under third party review. Additionally, the guidance documents do not address how differences in opinion between FDA staff and the third party reviewers will be adjudicated.

BIO recommends that FDA prospectively establish or identify the process by which it will ensure that the same standards for review are used across different products and reviewers. Further, FDA should articulate the process and standards by which disagreements between FDA staff and third party reviewers will be adjudicated. To the extent possible, FDA should contract with third parties to do reviews in collaboration with and under the direction of FDA. It is important that these reviews do not occur in a "vacuum" vis-à-vis interaction with the Agency.

X. FDA Should Provide Guidance Regarding How Marketing Claims Will Be Managed

As FDA noted in the Federal Register Notice announcing the availability of the LDT Guidances, technological advances have increased the use of diagnostic devices in guiding critical clinical management decisions for high risk diseases and conditions, resulting in FDA's proposal for additional FDA oversight. BIO recommends that FDA update and include in the framework guidance its policies regarding marketing claims to promote a test that would inform therapeutic treatment decisions.

XI. FDA Should Develop and Post a Communication Plan for Stakeholders During the Transition Period

Because of the complexity of the issues and to ensure that all stakeholders clearly understand the regulatory requirements for their LDTs, BIO recommends that FDA develop and post a communication plan to be implemented during the transition period that includes frequent updates and explanations about pertinent matters, tools for stakeholder use such as checklists or flow charts, as well as opportunities for FDA to respond publicly to questions from stakeholders. For example, FDA communications could provide specific dates that FDA will initiate activities that are predicated on the completion of earlier phases of implementation, such as when Class III and Class II phased- in enforcement of premarket review and QSR will begin; and when registration will be required for each LDT category.

XII. FDA Should Consider Whether the Release of a Second Draft of the LDT Guidances with Another Comment Period Is Necessary to Ensure that Stakeholder Feedback is Optimally Integrated

The proposal for FDA to end its enforcement discretion toward LDTs is a substantial change in policy that, while well intentioned, has the potential to threaten patient access and continued innovation for molecular diagnostics if not carefully calibrated and implemented. As highlighted above, FDA and stakeholders benefited from the Agency's call for comment at the 2010 workshop. Although the draft LDT Guidances address many of the principles and concerns raised by stakeholders raised at the workshop, questions of significance remain. Consistent with FDA's Good Guidance Practices and the Agency's statements regarding these guidance documents, BIO recommends that FDA consider whether a second draft of the LDT Guidances would be

beneficial and necessary to achieving the Agency's goal of protecting patient safety and ensuring the availability of high quality LDTs. Additionally, as also requested above, BIO believes that draft guidance documents on risk classification for LDTs, regulation of next generation sequencing, "me too" companion diagnostic devices, and LDT compliance with QSR should be published as soon as possible.

****

As noted above, BIO supports patient access to high-quality, innovative diagnostic tests for actionable biomarkers. The proposed regulatory plan will impose additional costs to LDT developers. BIO encourages FDA to consider supporting the development of incentives to encourage LDT developers to adopt the new approach quickly, and to support Congressional activities around such incentives. Examples of such incentives (which should apply equally to traditional IVD manufacturers) might include earlier reimbursement eligibility and special market protections.

BIO appreciates the opportunity to provide these comments, and would be happy to work with the Agency to address any of the concerns raised herein.

Sincerely,

Paul Sheives, JD
Director, Diagnostics and Personalized Medicine Policy