Biotechnology Industry Organization

March 20, 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 in association with FDA's public meeting entitled *Optimizing FDA's Regulatory Oversight of Next Generation Sequencing Diagnostic Tests*. BIO is the world's largest trade association representing 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 biotechnology products. Specifically related to next generation sequencing (NGS), BIO represents both companies that develop and market NGS technologies and therapeutic developers with pipeline products that use NGS as a companion diagnostic platform. For this reason, BIO welcomes the opportunity to work with the FDA on the development of policy in this area.

BIO commends the FDA for prospectively seeking input from industry to ensure that the regulatory environment is supportive of the rapid technological advancements of NGS tests. This technology continues to advance our scientific knowledge and capability in the area of genomics, and also positively impact the care of patients. As with other such transformative technologies, the implementation of regulation will present acute regulatory challenges. Consequently, FDA's current regulatory pathways are not well suited to assess NGS technology, and will certainly create further challenges as the pace of development continues to accelerate.

In addition to the FDA's admirable effort towards ensuring that the regulation of NGS technologies does not serve as a barrier to innovation, BIO encourages FDA to apply in the future what it learns regarding optimizing regulation for NGS and apply it to other large-scale, multi-plex

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technologies that present similar challenges. With the increasing clinical relevance of proteomics, metabolomics, lipidomics, and other existing high-throughput multi-plex genomic technologies (*e.g.*, genomic arrays), it is critical that the Agency evaluate regulatory approaches that also seek to optimize regulatory efficiency and allow continued innovation in these areas. BIO would be pleased to work with the FDA to address regulation in these product areas as well.

BIO appreciates the FDA's diligence on the regulation of molecular diagnostics, and recognizes that the NGS regulatory approach will be an important piece to the overall regulation. Accordingly, BIO believes that it is important to address outstanding regulatory issues in concert. As stated in BIO's comments on the draft guidance documents published by the FDA on the regulation of laboratory-developed tests (LDTs), BIO recommends that the Agency strive to publish – as close to in unison as possible—the guidance documents on LDT regulation, risk classification for LDTs, "me too" companion diagnostics (including any guidance for companion diagnostics where the referenced product has an established companion diagnostic), and next generation sequencing. For example, FDA should clarify companion diagnostic considerations in the proposed regulation for NGS tests. Where an NGS result includes a known marker that is listed as a companion diagnostic in an approved drug or biologic label, FDA should clarify how such a NGS test will be regulated, and how it fits into the FDA's proposed framework for the regulation of LDTs.

1. Specific Comments Relating to the Regulation of Analytical Validity and Performance of NGS

With regard to the regulation of the analytical validity of NGS, the FDA should ensure that appropriately-tailored oversight provides adequate flexibility to address both the significant variability among existing platforms and the continued evolution of this technology in the coming years. BIO agrees with FDA's approach to approve/clear particular NGS platforms or systems, and that an approach for assessing analytical validity based on certification and standards may be appropriate to ensure a dynamic approach that protects patient safety and ensures effective products in the context of the claims associated with the product or service. However, it will be important to define which body will set the standards, and contemplate the potential impact where

individual laboratories and manufacturers have their own methods and software to ensure validation. Although this approach will increase the efficiency of bringing products to the market, BIO is concerned that the time it takes to approve or clear these products will not keep pace with product offerings. In these cases, platforms sold for research purposes may be significantly more powerful or accurate than those approved/cleared for use in a clinical setting, or may not be approved/cleared for use in a particular clinical application.

Similar to the BIO's comments on FDA's proposed LDT framework, we encourage FDA to consider any overlap and potential for conflict with the Clinical Laboratory Improvement Amendments (CLIA). The Discussion Paper does not make any reference to CLIA regulations, and how they might potentially relate to FDA's regulatory approach to NGS. More specifically, both FDA and CLIA will require the establishment of analytical performance for NGS tests. (We note that the College of American Pathologists has also issued guidance with such requirements). While FDA's proposed approach will focus on establishing analytical performance of the NGS method, CLIA regulations will require clinical laboratories to establish analytical performance specifications for each NGS based LDT test prior to releasing any test results. Accordingly, it is important for FDA to consider any intersections between these regulatory approaches by the Agency and the Centers for Medicare & Medicaid Services (CMS).

Lastly, with regard to LDTs developed using NGS, FDA should clarify whether the risk under the classification provisions the FDA's proposed LDT regulatory framework would decrease if the LDT were performed on an FDA approved/cleared platform.

2. Specific Comments Relating to the Regulation of the Clinical Validity and Performance of NGS

NGS tests are distinct from targeted sequencing *in vitro* diagnostic tests, because the technology holds the potential to assess a less defined or manageable set markers than historical molecular diagnostics. Although the data set is limited by the number of variants that could be detected in the entire genome (or the boundaries of a targeted NGS panel with defined amplicons to detect pre-specified targets), BIO agrees with

FDA's concern that it is impractical for the Agency to assess the clinical validity of *every* possible genetic variant that could be detected by a platform. Accordingly, the FDA should exercise a flexible approach that facilitates NGS testing into clinical decision-making by allowing test developers to make modifications within a single NGS instrument, as necessary. BIO understands FDA's concern regarding the lack of specific intended use for some of the data generated by NGS, and the potential it creates for incidental findings. However, BIO believes that the best approach is for the FDA to focus on ensuring the analytical validity of the NGS platform, and assess new variants based on an approach that balances the need for evidence of safety and effectiveness with the pace of innovation.

BIO appreciates FDA's consideration of an approach that would leverage well-curated, third-party databases to assess the clinical performance of NGS tests as an alternative to conducting new studies. The FDA should continue to provide test developers with flexibility as it continues to consider a broader approach to ensuring the accuracy and reliability of evidence on the strength of association between variants and disease. As part of the guidance, BIO recommends that the FDA provide a description of what the Agency views as a "well-curated database" and specify a minimum set of criteria or metrics for third party database developers/curators to follow. BIO also notes that the Discussion Paper does not address FDA contemplates a single database or a set of disease specific databases, and that this should be given consideration in the draft guidance document.

Consistent with our comments above concerning platforms other than NGS, FDA recognizes that other technologies capable of detecting genetic variation, including but not limited to polymerase chain reaction (PCR) and single-nucleotide polymorphism (SNP) arrays, may benefit from a different approach for capturing data related to clinical performance. FDA's approach for leveraging curated genetic databases to evaluate clinical performance should be utilized equally across all technologies capable of detecting genetic variation. BIO encourages FDA to consider how to apply this approach following its application in the NGS product and service space. In addition, FDA should ensure that the clinical review of molecular tests developed by traditional IVD

manufacturers allows for the same use of this evidentiary resource, such that this approach does not only apply to services performed as a LDT.

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BIO agrees with the FDA that it is critical to implement efficient and appropriate oversight of NGS tests, while ensuring their safety and efficacy. FDA should work closely with all stakeholders to develop methodological, quality-based standards that laboratories and IVD manufacturers could meet to ensure accuracy and reliability, but also flexibility that allows further innovations in the field. 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