ASSOCIATION FOR MOLECULAR PATHOLOGY
Education. Innovation & Improved Patient Care. Advocacy.
9650 Rockville Pike, Suite 205, Bethesda, Maryland 20814
Tel: 301-634-7939 | Fax: 301-634-7995 | amp@amp.org | www.amp.org

March 19, 2018

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2017-N-6356, Investigational In Vitro Diagnostics Used in Clinical Investigations of Therapeutic Products; Draft Guidance for Industry, Food and Drug Administration Staff, Sponsors, and Institutional Review Boards

Submitted electronically at www.regulations.gov

To whom it may concern:

The Association for Molecular Pathology appreciates the opportunity to provide comments on the draft guidance on Investigational In Vitro Diagnostics Used in Clinical Investigations of Therapeutic Products; Draft Guidance for Industry, Food and Drug Administration Staff, Sponsors, and Institutional Review Boards (FDA-2017-N-6356). AMP is an international medical and professional association representing approximately 2,400 physicians, doctoral scientists, and medical technologists who perform or are involved with laboratory testing based on knowledge derived from molecular biology, genetics and genomics. Membership includes professionals from the government, academic medicine, clinical testing laboratories, and the in vitro diagnostics (IVD) industry. Our members' have considerable experience in providing patient care through performing thousands of laboratory procedures in clinical settings.

AMP appreciates the goal of FDA to provide stakeholders, including institutional review boards (IRBs), with more information in making determinations as to whether an IVD is investigational. However, AMP is concerned that this guidance document provides unclear information regarding when molecular laboratory tests are subject to the Food and Drug Administration's (FDA's) Investigational Device Exemption (IDE). Below we provide recommendations to aid in refining the guidance document to assist clinical investigators working to improve patient care.

Laboratory developed testing procedures do not fall within the definition of an investigational IVD

While this guidance document does not directly mention laboratory developed testing procedures (LDPs), there are numerous instances within the draft guidance in which FDA conveys information that suggests that LDPs are investigational. For instance, FDA states in footnote 13 that a legally marketed IVD is "one that is approved, cleared, or Class I or Class II exempt" which insinuates that all LDPs that have been evaluated by other entities are not legally marketed. On the contrary, not only are LDPs appropriately and legally used in clinical practice, often they are considered the standard of care.

As FDA is aware, every laboratory performing clinical testing is certified by the Clinical Laboratory Improvement Amendments (CLIA) program in the Centers for Medicare & Medicaid Services (CMS) which assures laboratory

performance standards and the tests' accuracy and reliability. Additionally as part of the requirements outlined under CLIA, laboratories performing high-complexity tests must undergo regular proficiency testing to ensure that laboratories are meeting specific standards in an ongoing manner. Many laboratories obtain CLIA certification through accreditation by CMS-approved accrediting agencies such the College of American Pathologists (CAP) or the Joint Committee on Hospital Accreditation, or obtain CLIA certificates through licensure from CLIA exempt states. The standards of the accreditation program or state in aggregate must meet or exceed those of the CLIA regulations. The programs often go well beyond the mandates within CLIA including more stringent requirements for proficiency testing, as well as documentation of clinical validity. One of these state-based programs operated by the New York State Department of Health was also recently was accredited as an FDA third party reviewer and thus, is clearly able to perform the necessary duties to assure accuracy and precision of molecular tests.

Laboratories offering LDPs for clinical care should adhere to both federal and state requirements, and if so, a laboratory's LDPs are not investigational because the laboratory would have demonstrated assurances of accuracy and precision to entities other than the FDA. Therefore, LDPs do not by default fall within the definition of an investigational IVD.[1] This is also the case for LDPs developed by certified laboratories when they modify a cleared or approved IVD. Modifications to IVD kits are made to adapt a test for the laboratory context and the population that a laboratory serves and are also subject to the same regulatory requirements that are outlined above.

Recent publications in peer-reviewed journal elucidate findings to address whether there are performance differences between LDPs and FDA-reviewed IVDs. These findings, based on information gleaned from actual proficiency testing outcomes, indicate that LDPs perform similarly to IVDs. Kim and colleagues (2017) analyzed 6,897 proficiency testing responses from 2011-2015 and found that both LDPs and FDA IVDs performed well exceeding 97% accuracy for the genes *BRAF*, *EGFR*, and *KRAS* combined.[2] The authors noted that more than 60% of participants using an FDA-reviewed test adapted the test to accommodate patient need. This involved making modifications to allow for a greater breadth of sample types, minimalizing tumor sample size, and instrumentation. Additionally, Kaul and colleagues (2017) reported that LDPs used to detect herpes simplex virus detection by polymerase chain reaction performed with a high degree of accuracy based on the responses from 383 laboratories -- an overall accuracy of 99.4% was obtained.[3] These types of findings further support the notion that LDPs are not simply investigational by default. Thus, FDA should not automatically apply IDE requirements to LDPs used for a clinical purpose by CLIA-certified laboratories.

The draft guidance should better distinguish risk among clinical trial phases

Further, clinical trials involving both an investigational therapy and an investigational test that utilizes a companion analyte are becoming more commonplace and it is important that investigators understand FDA's strategies for assessing levels of risk. The guidance document does not make a distinction of risk between phase I, II, and III clinical trials. Much more information about dose and toxicity is understood after phase I testing, yet, as FDA notes, whether a test is considered a significant risk or not depends on these aspects of the treatment. The guidance lacks clarity as to how a laboratory can accurately predict what the risk of the therapy will be for

[1] 21 CFR 812.3(g)

[2] Kim AS, Bartley AN, Bridge JA, Kamel-Reid S, Lazar AJ, Lindeman NI, Long TA, Merker JD, Rai AJ, Rimm DL, Rothberg PG, Vasalos P, Moncur JT. Comparison of Laboratory-Developed Tests and FDA-Approved Assays for BRAF, EGFR, and KRAS Testing. JAMA Oncol. Published online December 14, 2017. doi:10.1001/jamaoncol.2017.4021

[3] Kaul KL, Sabatini LM, Tsongalis GJ, et al. The Case for Laboratory Developed Procedures: Quality and Positive Impact on Patient Care. Academic Pathology. 2017;4:2374289517708309. doi:10.1177/2374289517708309.

the study patient population. Stakeholders would benefit from further information on FDA thinking's on the topic. AMP recommends that FDA explicitly indicate within the draft guidance whether the agency is referring to the risk of the therapy versus the risk of the test in the guidance document.

FDA should address the potential level of burden an IDE requirement could have on research, innovation, and precision medicine

Additionally, AMP requests that FDA ensure the IDE review process is streamlined for laboratory tests that are truly investigational. AMP is concerned that the IDE review requirements are quite arduous, especially for professionals not familiar with the process, and as a result such processes could place an enormous burden on investigators. It some cases, IDE review has delayed research projects significantly and taken away an enormous share of financial resources originally awarded to account for costs of the actual research project. For example, during a session devoted to this topic at the American Society of Human Genetics Annual Meeting in 2017, Jonathan Berg, Assistant Professor at the University of North Carolina at Chapel Hill described how applying for an IDE for the BabySeq Project delayed his research by over a year and drained resources intended for funding the research itself.

In order to ensure efficient use of government research funds, AMP recommends that FDA work with the National Institutes of Health (NIH) to develop a streamlined process to minimize the impact on the research timeline. Further, FDA and NIH's actions to streamline this process and their developed guidance materials should be used as a model for other Federal agencies funding clinical research that uses investigational tests. A no-cost extension may need to be provided to researchers depending on the length of time FDA takes to review an IDE. In addition, FDA and NIH should consider the funding requirements for IDE review and include those additional funds in the total funds provided for the project. Lastly, because many professionals are not familiar with the FDA IDE process, AMP recommends that FDA and NIH collaborate to provide clinical investigators with guidance on these topics.

Thank you for your consideration of these comments. If you have any questions, please contact Tara Burke, AMP's Director of Public Policy and Advocacy at 301-634-7939 or at tburke@amp.org.

Sincerely,

Kojo S.J. Elenitoba-Johnson, MD
President, Association for Molecular Pathology