King & Spalding
Client Alert

JUNE 25, 2018

For more information, contact:

Kyle Sampson
+1 202 626 9226
ksampson@kslaw.com

Lisa M. Dwyer
+1 202 626 2393
ldwyer@kslaw.com

David J. Farber
+1 202 626 2941
dfarber@kslaw.com

King & Spalding

Washington, D.C.
1700 Pennsylvania Avenue, NW
Washington, D.C. 20006-4707
Tel: +1 202 737 0500

FDA Classifies Next Generation Sequencing-Based Tumor Profiling In Vitro Diagnostic Into Class II (Special Controls)

Last week, the U.S. Food and Drug Administration (FDA) issued a final order classifying in vitro diagnostic (IVD) tests that utilize next generation sequencing (NGS) to profile cancer tumors into Class II (special controls). In the order, FDA named the generic type of device "Next Generation Sequencing Based Tumor Profiling Test" and described it as a qualitative IVD test "intended for NGS analysis of tissue specimens from malignant solid neoplasms to detect somatic mutations in a broad panel of targeted genes to aid in the management of previously diagnosed cancer patients by qualified health care professionals." FDA, Final Order, *Medical Devices; Immunology and Microbiology Devices; Classification of the Next Generation Sequencing Based Tumor Profiling Test*, 83 Fed. Reg. 28,994, 28,994-95 (June 22, 2018). FDA codified the classification at 21 C.F.R. § 866.6080.

The practical effect of FDA's De Novo classification order is that the specific device that was classified—the MSK-IMPACT (Integrated Mutation Profiling of Actionable Cancer Targets) test developed by Memorial Sloan-Kettering Cancer Center's Department of Pathology—now can serve as a predicate for future devices of the same type, including for premarket notification submissions under Section 510(k) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). *See* 21 U.S.C. § 360c(f)(2)(B)(i). As a result, other developers of similar NGS-based IVD tests will not have to submit a De Novo classification request or premarket approval (PMA) application in order to market a substantially equivalent device. *See id.* § 360c(i) (defining ''substantial equivalence''). Instead, such device sponsors can use the less-burdensome 510(k) process to market their device.

In evaluating whether NGS-based tumor profiling IVD tests could be classified into Class II, FDA considered two specific health risks: (1) incorrect performance of the test leading to false positives or false negatives; and (2) incorrect interpretation of test results. Ultimately, FDA

determined that there is a reasonable assurance of safety and effectiveness for NGS-based tumor profiling IVD tests that conform to the general and special controls established in the new regulation. Among other things, the controls established in the new regulation require that premarket notification submissions (i.e., 510(k) submissions) for NGS-based tumor profiling IVD tests include information about: "all somatic mutations that are intended to be detected by the test"; the indications for use (which must be limited to "previously diagnosed cancer patients" and identify the specific "testing facility or facilities" performing the test); and the "genomic coverage" of the test. *See* 21 C.F.R. § 866.6080(b)(1)(i)-(iii). In addition, special controls include certain labeling requirements, including categorization of all somatic mutations reported in the test results as either "cancer mutations panel with *evidence of* clinical significance" or "cancer mutations panel with *potential* clinical significance." *Id.* § 866.6080(b)(2)(iv) (emphases added).

To address the concern about incorrect interpretation of test results, 510(k) submissions for NGS-based tumor profiling IVD tests also must include a "list of links provided by the device to the user or accessed by the device for internal or external information (e.g., decision rules or databases) supporting clinical significance of test results for the panel." *Id.* § 866.6080(b)(1)(iii)(E). For mutations under the category of "cancer mutations panel with evidence of clinical significance," device labeling and test reports must include links "for physicians to access information concerning decision rules or conclusions about the level of evidence for clinical significance that is associated with the marker" detected. *Id.* § 866.6080(b)(2)(vi).

FDA's action last week comes on the heels of the agency's issuance in April of two guidance documents intended to promote "FDA's vision . . . that NGS-based tests can be developed, validated, and offered for clinical use through a process that leverages appropriate standards, quality systems controls and community assessment of clinical validity to streamline the premarket review process." FDA, Guidance, *Considerations for Design, Development, and Analytical Validation of Next Generation Sequencing (NGS)-Based In Vitro Diagnostics (IVDs) Intended to Aid in the Diagnosis of Suspected Germline Diseases* § I (Apr. 13, 2018) [hereinafter "*NGS-based IVD Guidance*"].

The first guidance, the *NGS-based IVD Guidance*, provides recommendations for designing, developing, and validating NGS-based tests used to diagnose individuals with suspected germline (i.e., genetic) diseases. It describes what the FDA would look for in 510(k) submissions to determine a test's analytical validity, including how well the test detects the presence or absence of a particular genomic change. The guidance notes that

> FDA believes the recommendations in this guidance and/or standards that address these recommendations may potentially form the basis of special controls that could reasonably assure the safety and effectiveness (which, for IVDs, generally means a reasonable assurance of analytical and clinical validity) of these tests, allowing NGS-based tests intended to aid in the diagnosis of suspected germline diseases to be candidates for classification as Class II devices via the De Novo process. If classified in class II, subsequent NGS-based tests intended to aid in the diagnosis of suspected germline diseases would be reviewed through the 510(k) program . . . .

Id. Although the *NGS-based IVD Guidance* does not, by its terms, apply to NGS tests intended to identify somatic mutations, *see id.* § III, FDA's De Novo classification of the Memorial Sloan-Kettering MSK-IMPACT test indicates that FDA is willing to open up a more streamlined 510(k) pathway for NGS tests intended to identify somatic mutations. Indeed, the De Novo classification of the MSK-IMPACT test is an exemplar of the agency's efforts to reduce regulatory burdens on developers of NGS-based tests. *Compare* 83 Fed. Reg. at 28,994-95 (classifying the MSK-IMPACT NGS-based tumor profiling IVD test into Class II and noting that "the device can serve as a predicate for future devices of that type, including for 510(k)s"), *with NGS-based IVD Guidance* § IV (noting that "there are currently no legally marketed devices of the same type that could serve as a predicate device for review of . . . NGS-based test[s for the diagnosis of suspected germline diseases] in a premarket notification under section 510(k)").

The second guidance issued in April, *Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based In Vitro Diagnostics* (Apr. 13, 2018) [hereinafter "*Genetic Variant Database Guidance*"], describes how IVD test developers may rely on clinical evidence from FDA-recognized public databases to support clinical claims for their tests and help provide assurance of the accurate clinical evaluation of genomic test results. The *Genetic Variant Database Guidance* describes how product developers can use these databases to support the clinical validation of the NGS tests that they are developing. It also describes a process that administrators of genetic variant databases can follow in order to obtain FDA recognition.

As noted, the specials controls associated with FDA's classification of Memorial Sloan-Kettering's MSK-IMPACT test into Class II requires NGS-based tumor profiling IVD tests to reference clinical validity information, including clinical validity information contained in an FDA-recognized genetic variant database. *See* 21 C.F.R. § 866.6080(b)(1)(iii)(E) (requiring 510(k) submissions for NGS-based tumor profiling IVD tests to reference "internal or external information (*e.g.*, decisions rules or databases) supporting clinical significance of test results"); *id.* § 866.6080(b)(2)(vi) (requiring labeling for NGS-based tumor profiling IVD tests to contain "link(s) for physicians to access . . . information concerning decision rules or conclusions about the level of evidence for clinical significance that is associated with the marker"). Likewise, it can be expected that FDA classification of an NGS-based test for the diagnosis of suspected germline diseases into Class II will similarly require 510(k) submissions and approved labeling for such IVDs to reference clinical validity information, including such information contained in FDA-recognized genetic variant databases.