FAQs for Third Party Review Process for Next Generation Sequencing Oncology Panels

If a laboratory (sponsor) also tests for copy number variants (CNVs), structural variants (SVs) and tumor mutation burden (TMB), all on the same platform, can the New York State Department of Health (NYSDOH) still review the sponsor's assay under the 3rd party review process, but consider only the variant types that are cleared as part of the MSK-IMPACT assay for substantial equivalence? Would the sponsor be able to report on all of the variants in their assay, but with distinct disclaimers as to which are FDA cleared and which are only NYSDOH approved?

Assays reporting other variant types not included in the MSK-IMPACT de novo review (such as CNVs, SVs and TMB) are also covered under the same regulation and thus eligible for 510(k) review. However, given that the analytical validation requirements for those additional variant types have not been established yet, FDA recommends that sponsors submit a pre-submission to determine what data would be needed to support those claims prior to a 510(k) submission. Alternatively, if they request third party review through NYSDOH, FDA would expect for NYSDOH to work with them to establish the validation acceptance criteria before authorizing any assays with these new variant type claims.

If a sponsor also seeks clearance for variant types not included in the MSK-IMPACT assay, would they be required to submit a de novo 510(k) submission directly to the FDA?

Sponsors may also choose to submit only validation data for variant types covered in the MSK-IMPACT assay (SNVs, small insertions and deletions, MSI) first to obtain 510(k) clearance limited to those variant types only (sponsors can still report other variant types using the "non-FDA cleared" LDP version of the test). Once the FDA has established the validation standards for other variant types with NYSDOH these new variant types may also be cleared through 3rd party review process.

Since NYSDOH grants assay approval, but with a requirement for ongoing confirmation of variants when full validation has not been completed, would a sponsor be required to reach full validation status under NYSDOH requirements before the assay can be considered for 3rd party review?

Yes, full validation would be required as per NYSDOH guidelines prior to FDA clearance being granted.

The MSK-IMPACT predicate device (assay) is analyzed on the Illumina HiSeq 2500 platform. Would a sponsor's assay using a different platform, either from Illumina (e.g. Novaseq) or Thermo Fisher (e.g. Ion S5) be eligible for 3rd party review?

Yes, assays analyzed on other NGS platforms are eligible for 3rd party review.

The MSK-IMPACT assay is cleared for SNVs, small insertions and deletions, and MSI on the Illumina Hiseq 2500 instrument. If a sponsor only analyzes MSI on the Illumina platform, but analyzes SNVs and insertions and deletions on a Thermo Fisher instrument, is the sponsor's assay eligible for 3rd party review? Presumably these would be considered two separate devices with the requirement of separate reviews.

Yes, these would be considered two separate devices (i.e., different test panels) and they would be reviewed separately. Please note the MSI testing covered by MSK-IMPACT authorization is only for tumor profiling use; if a sponsor is seeking other MSI claims (e.g. screening for Lynch syndrome or companion diagnostic claim), then the device is not eligible for tumor profiling 510(k).

Can an assay that went through the PMA review process, such as Foundation Medicine's F1CDx or Thermo Fisher's Oncomine panel, be used as the predicate device for 3rd party review?

No, the predicate device must be class 2.

Does a sponsor's assay need to be compared directly to MSK-IMPACT for 3rd party review and FDA clearance?

MSK-IMPACT is what is referred to as a "paper predicate", meaning that actual comparison to the predicate is not needed for establishing accuracy etc. For the tumor profiling claim, the orthogonal method used for accuracy could be another validated test.

If an NGS assay includes both solid and hematological tumors in its claims of intended use, would it be eligible for 3rd party review with the MSK-IMPACT as the predicate device or would it be required to be split into two separate devices?

If the hematological assay only analyzes variant types present in the MSK-IMPACT assay then it may be eligible for 3rd party review. However, given that heme tumor profiling is currently outside the MSK-IMPACT's authorized intended use, we are recommending that sponsors have a pre-submission discussion with us. FDA's concern regarding heme tests is that many biomarkers are for diagnostic use with cutoffs established with other technologies such as FISH. Further, heme biomarkers are often structural variants (CNVs, fusions) which the MSK-IMAPCT test does not have claims for at this time.

Would FDA expect different quality metrics for a hematological assay?

Quality metrics may be different and should be established by the sponsor as part of the test optimization. In addition, the validation requirements may be different. For example, concordance to clinically validated FISH methods is recommended.

If combining the solid and hematological parts in one assay is acceptable, would an uneven split, e.g. 40:60, in sample numbers be acceptable?

Independent quality metrics for sample input would need to be established for both solid and hematological tumors. Validation would be performed at the gene level for all intended variant types and sample types. Please also see the responses above. FDA considers the heme part a new indication likely with different special controls, and thus it would need to be validated independently.

If a sponsor submits an assay with a large number of genes and gets clearance, can the sponsor then market subpanels under the same clearance (analytically the same test but with bioinformatic masking of some data)?

Yes, subpanels are acceptable if analytically they are processed identically to the cleared assay (i.e. same wet lab process, same analysis pipeline and cutoffs, etc.) and the subpanels are only based on downstream software selection (masking).

If a sponsor submits an assay covering a different number of genes, or genes not included in the MSK-IMPACT assay, is the sponsor's assay eligible for 3rd party review?

Yes. Not all genes covered by MSK-IMPACT must be covered in the sponsor's assay and not all genes covered by the sponsor's assay must on the MSK-IMPACT panel; panels of any size would be accepted for review under this regulation.