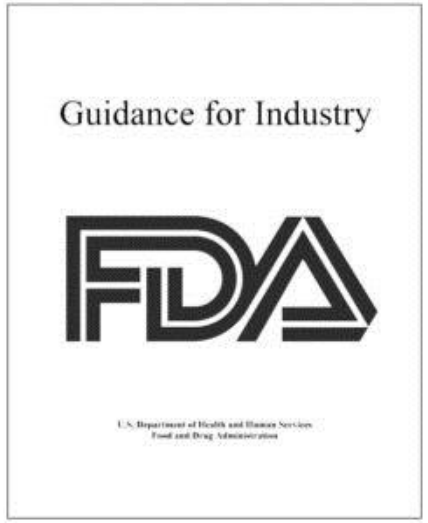

A Year in Review: Noteworthy FDA Guidances and Rules for IVD Companies

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Considerations for Design, Development, and Analytical Validation of NGS

FINALS ISSUED

APRIL 13, 2018

- Significantly modified from the draft.
- Limited scope going from all NGS-based tests to only those intended to diagnose suspected germline diseases in symptomatic patients.
- Provides detailed guidance regarding analytical validation, assessing changes, as well as other important topics.
- Likely de novo, although shortened discussion of the possibility that FDA would classify such tests as 510(k)-exempt

Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based *In Vitro* Diagnostics

FINALS ISSUED

APRIL 13, 2018

- Virtually unchanged from the draft guidance, issued July 8, 2016.
- Describes FDA's considerations in determining whether a publicly available genetic variant database can serve as a source of valid scientific evidence to support the clinical validity of an NGS-based test in a premarket submission.
- Describes the process by which administrators of such databases can voluntarily apply to FDA for recognition.

First Formal Recognition

- On December 4, 2018, FDA recognized the first public database containing information about genes, genetic variants, and their relationship to disease.
- Clinical Genomic Resource (ClinGen) consortium's ClinGen Expert Curated Human Genetic Data.
- Limited recognition "for germline variants for hereditary disease where there is a high likelihood that the disease or condition will materialize given a deleterious variant (i.e., high penetrance."

Consideration of Uncertainty in Making Benefit-Risk Determinations in Medical Device Premarket Approvals, De Novo Classifications, and Humanitarian Device Exemptions

DRAFT GUIDANCE

SEPTEMBER 6, 2018

Factors to Consider:

1. Probable benefits;
2. Probable risks;
3. Uncertainty regarding the benefit-risk profile;
4. Patient perspective;
5. Public health need;
6. Feasibility of generating extensive premarket data;
7. Ability to reduce or resolve uncertainty;
8. Likely effectiveness of postmarket mitigations (e.g., labeling);
9. Type of decision being made (e.g., more uncertainty is acceptable for HDEs than PMAs); and
10. Probable benefits of earlier patient access.

De Novos

- Probable risks will play a large role in analyzing uncertainty
- Uncertainty of probable benefit can be mitigated if the risks are minimal or through imposition of special controls.

- Uncertainty connected to amount of clinical data required
  - Examples include breakthrough devices and devices with small patient populations
  - IVD-specific example included
- Correlates the level of uncertainty with the statistical confidence from a submission's clinical study
- Greater the uncertainty the greater the need for post-market data

Multiple Function Device Products: Policy and Considerations

DRAFT GUIDANCE

APRIL 27, 2018

- Intended to clarify how FDA assesses the impact of functions that are not subject to FDA review when they are part of a multi-function product that includes at least one function subject to FDA review.
- FDA will consider:
  - Whether the other function(s) may impact the safety or effectiveness of the device function-under-review.
  - Whether there are shared computational resources, data dependencies, or any other type of relationship between the functions.
- If the other function(s) may impact the safety or effectiveness of the device function-under-review, FDA will consider whether there is an increased risk or adverse effect on performance.
- Primarily related to software, but could reasonably be applied to IVDs as well

Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications (510(k)) with Different Technological Characteristics

FINAL GUIDANCE

SEPTEMBER 25, 2018

510(k) Review Process

- Do the new device and predicate device have the same intended use?
- Are there technological differences, and if so, do those differences raise different questions of safety or effectiveness?
- If no different questions of safety or effectiveness, FDA will then review test methods and data to determine if the data demonstrate substantial equivalence.

The benefit-risk profile of a new device *does not* need to be identical to be as safe and effective as the predicate device.

Risk/Benefit Profile	Assessment Needed?
Increased/Equivalent Benefit Decreased/Equivalent Risk	No
Increased Risk Increase/Equivalent Benefit	Yes
Equivalent Risk Decreased Benefit	Yes
Increased Risk Decreased Benefit	No
Decreased/Equivalent Risk Decreased Benefit	Yes

Select Updates for Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of *In Vitro* Diagnostic Devices

Recommendations for Dual 510(k) and CLIA Waiver by Application Studies

DRAFTS RE-ISSUED NOVEMBER 29, 2018

- The overall requirements and framework of the guidances have not changed substantively since 2017, but virtually all illustrative examples were removed.
- Leaves open the possibility that a clinical study is not required to establish waived status.
- CLIA Waiver Guidance: *Four* options for demonstrating waiver, providing additional flexibility in study design
  1. Comparison of a candidate test in the hands of trained and untrained users;
  2. Assay migration study design;
  3. Flex and human factors studies alone; and
  4. Comparison of a candidate test in the hands of untrained users compared to a comparator method in the hands of trained users.

Voluntary Malfunction Summary Reporting Program for Device Manufacturers

FINAL RULE

ISSUED AUGUST 17, 2018

- Manufacturers of devices and device-led combination products can report certain device malfunctions for low-risk products in summary form on a quarterly basis, as an alternative to Medical Device Reporting requirements.
- Applies only to reporting of malfunction events by manufacturers
  - Not deaths or serious injuries, or
  - Events requiring reporting by importers or user facilities.
- Only pertains to certain devices whose product code has been in existence for at least two years.

Summary Malfunction Reporting Schedule

Reportable malfunctions or supplemental information that you become aware of during these timeframes:	***Must be submitted to FDA by:***
January 1 – March 31	April 30
April 1 – June 30	July 31
July 1 – September 30	October 31
October 1 – December 31	January 31

Additional Limitations

- Does not replace requirement to submit a 5-day report under 21 C.F.R. § 803.53(a).
  - Including subsequent reportable malfunctions of the same nature involving similar devices
- Devices that are the subject of a recall
- New types of reportable malfunctions
- FDA can revoke eligibility

De Novo Classification Process

PROPOSED RULE

ISSUED DECEMBER 4, 2018

- Structurally similar to the 510(k) regulation and the PMA regulation
  - Format and content of a de novo submission,
  - Procedures governing FDA's review, and
  - Grounds for denial.

- Several additional elements of the submission likely to increase the burden on applicants.
  - Gives FDA authority to inspect manufacturing facilities and clinical trial sites.
  - Bibliography of all published and unpublished reports on the device and any other information relevant to a device's safety or effectiveness;
  - Samples of the device and its components, if requested by FDA;
  - Advertisements for the device.

Questions?

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