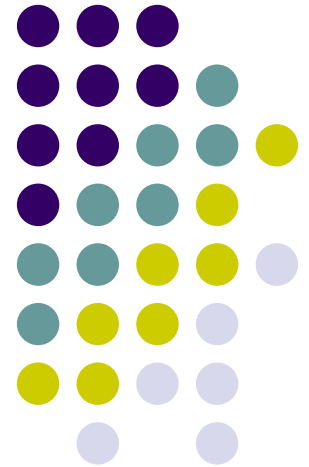


Novel Diagnostics: FDA Perspectives

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Regulation of Diagnostic Tests



- FDA regulates medical devices “intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals”
- Includes “reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae” aka IVDs.



General review issues

- intended use (e.g., to detect cytochrome P450 enzyme alleles)
- indications for use (e.g., predictive or prognostic for disease, treatment response, or drug sensitivity)
- methodology (e.g., polymerase chain reaction)
- technical interpretation of results (e.g., positive for variant alleles)
- quality control and assay limitations
- analytical performance (e.g., sensitivity, specificity, reproducibility)
- clinical validity (e.g., false positives and negatives)
- clinical interpretation
- benefits and risks
- claims made by the manufacturer (e.g., effectiveness)



Preanalytical issues

- Nature of specimen
 - Fresh-frozen, FFPE, blood, other
- Collection and handling
 - Collection device, matrix or stabilization method, time to stabilization
- Storage
 - Duration, conditions
- Characteristics
 - Percent tumor, necrosis, etc.



Instruments and reagents

- Instruments
 - Performance
 - Linearity, LoD, etc
 - Variability
 - Day-to-day, instrument-to-instrument
 - Calibration
- Reagents
 - Acceptance criteria
 - Stability

Software



- Firmware—controls instruments
- Signal conversion—converts raw signal into usable measurement
- Interpretive—applies interpretation rules to generate result

- Follow FDA software V/V recommendations

Analytical performance



- Test measures what you claim it measures
 - Genotyping arrays, CGH: comparison to another test or method, if available, e.g., sequence, karyotype, FISH, etc.
 - Expression arrays--a special case where analyte is the pattern: often no reference method
 - Others: Discuss with FDA

Repeatability/reproducibility



When measuring controls, samples over range of measurement:

- Repeatability or precision: repeated measurements under same conditions the same, e.g., triplicate measurements
- Reproducibility: different instruments, operators, lots, days, etc. yield same results

Interference/cross-reactivity

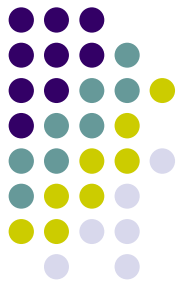


- Substances in specimen that cause false positive/false negative
- Other sequences that could interfere with signal
 - Design features, e.g., unique regions, sequence searches
 - Challenge, e.g., test with different concentrations of interferent/potential cross-reactive
 - Recommendations, e.g., avoid substances

Limits of sample



- Qualitative
 - Minimum amount of analyte or sample needed to reliably detect signal
 - Maximum amount of analyte or sample without saturation



Quality Controls

- Assurance that measurements are stable over time/detect failure
 - Extraction/purification
 - Conversion/amplification
 - Hybridization/signal
 - Positive/negative clinical samples
- Spike-in, endogenous in sample
- Corresponding probes on array

Clinical specimens



- Adequate information
 - How clinical truth determined
 - Population parameters, e.g., age, ethnicity, drug regimen, etc.
 - Collection/storage
 - Stability
- Unbiased selection
 - Tumor size
 - Disease stage

Clinical Validation Steps for Multivariate Assays



- Training Set(s)—intended use population
 - Develop classifier--explore classifiers, feature combinations
 - Cross Validation--LOOCV; 10-fold CV; Other variants
 - Lock down classifier—fix functions, features, cut-offs, etc.
 - Independent Validation—intended use population, pilot to size study
- Confirmatory studies w/Protocols

Statistical approaches

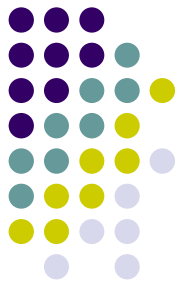


- Well-grounded assumptions
- Sufficient samples to reach predetermined goals
- Explanation of techniques, e.g., normalization strategies
- Rationale and data for cut-offs

Risk-based classification

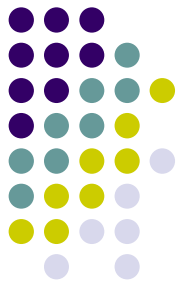


- Devices classified by FDA into
 - Class III—higher risk, present risk of injury or illness (to the patient or user)
 - Class II—moderate risk, general controls not sufficient, but can be mitigated through special controls
 - Class I—lower risk, little/no potential for unreasonable risk of injury or illness, general controls usually sufficient



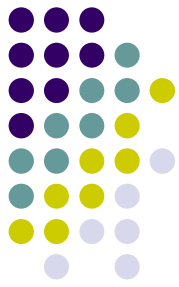
IVD Labeling

- Specific IVD labeling regs—21 CFR 809
- Particular focus of review
 - Intended use
 - Instructions for use, labels on products, etc.
- All parts of the system—instrument, reagents, other, to be labeled appropriately



Submission Types

- PreIDE—consultation prior to making regulatory submission
- 510(k)—substantially equivalent to existing predicate; usually comparison to another device or reference method
- De novo 510(k)—safe and effective for intended use, first of a kind, moderate risk
- PMA—safe and effective for intended use; usually comparison to “clinical truth”, high risk



Useful information

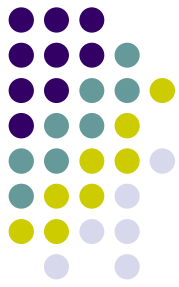
- STARD initiative
 - www.stard-statement.org
- FDA guidance documents
 - Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests
<http://www.fda.gov/cdrh/osb/guidance/1620.pdf>
 - Class II Special Controls Guidance Document: Gene Expression Profiling Test System for Breast Cancer Prognosis <http://www.fda.gov/cdrh/oivd/guidance/1627.pdf>
 - Many more

Information on cleared/approved IVDs-510(k)



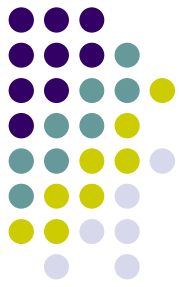
- OIVD Review Decision Summary
- 510(k) database
<http://www.fda.gov/cdrh/oivd/decisionsummaries.html>
- For de novo 510(k)s, Special Controls Guidance Documents available
 - Describes 510(k) submission requirements for devices of same type with same/similar intended use
 - <http://www.fda.gov/cdrh/oivd/index.html>

CDRH Device Advice



- Website with information on medical devices
 - Guidance
 - Regulations
 - Databases
- Good place to look for explanations of how to make submissions, pre- and post-market requirements
- <http://www.fda.gov/cdrh/devadvice/>

Office of In Vitro Diagnostic Device Evaluation and Safety



- OIVD was created in 2003 to address the complete life cycle of IVD tests—premarket and postmarket issues
- “One stop” shopping for IVD regulatory issues
- Cross-functional staff—premarket review, MDR review, recall assessment
- See it all here:
<http://www.fda.gov/cdrh/oivd/index.html>

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