Planning for the Regulatory Environment of your Life Sciences Startup

ENET

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Overview of Presentation

- Overview of FDA medical device regulations
- Outline IVD submission requirements
  - Traditional 510(k)
  - De Novo
  - CLIA Waiver
  - PMA
  - EUA
- Recent Trends
  - NextGen Sequencing
  - Nested Intended Use, Tier 1/2
  - Software algorithm - agnostic input (e.g. Digital Pathology)
  - Point of Care

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Intended Use

Example IVD

1. What the device detects − quantitative /qualitative, specific analyte/analytes [e.g. Her-2]
2. Technology used- Immunohistochemistry
3. Sample type − breast tissue
4. Patient population − CDx for Herceptin therapy for breast cancer
5. Any applicable contraindications

* Class III device

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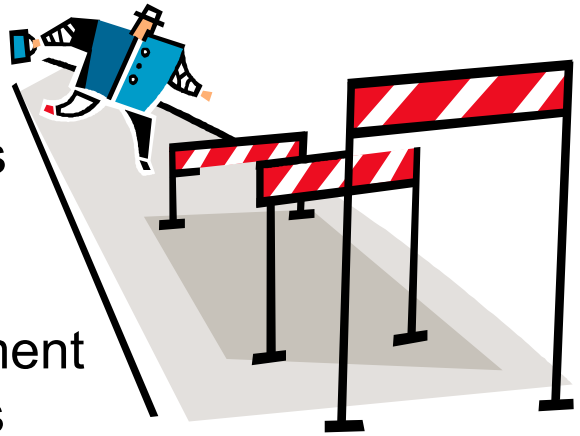
FDA Risk Classification

- **Class I**
  - General controls sufficient for
  - assurance of safety / effectiveness
- **Class II**
  - General controls insufficient
  - Sufficient information for development of standards and special controls
- **Class III**
  - General controls insufficient
  - Insufficient information for development of standards and special controls
  - Assessment of safety and effectiveness needed for reasonable assurance of safety and effectiveness



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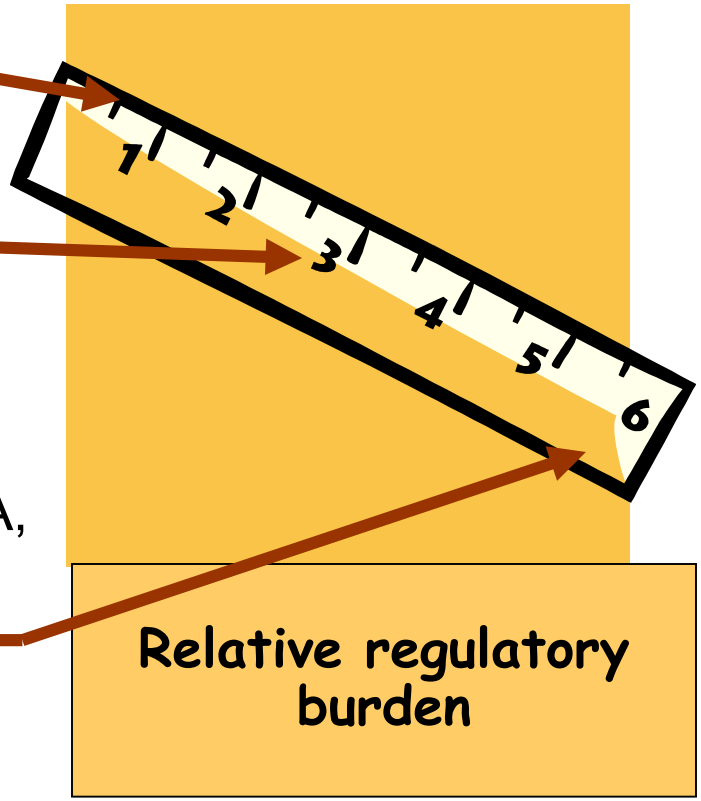
What is the impact of device Class on premarket regulatory burden?

- **Class I**
  - Exempt from pre-market notification unless specifically reserved
- **Class II**
  - 510(k) premarket notification - Traditional, Abbreviated, or Special
- **Class III**
  - Premarket approval application (PMA, PDP, or HDE) including clinical trial data
- **De Novo: 513(f)(2)**
  - Request for classification determination, benefit/risk, granted!



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Emergency Use Authorization

- FDA EUA website
  - https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#2019-ncov
- 37 Test Kits (as of 4/16/20)
  - 34 Molecular Tests
  - 3 Serology IgM/IgG
- 15 Laboratory Developed Tests (e.g. MGH)
- 27 Ventilators
- 4 Reprocess N95 Respirators
- 4 Respirators/Face Shields

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EUA Requirements

- Face Masks
  - The product meets fluid resistance testing (liquid barrier performance) consistent with standard ASTM F1862
  - meets Class I or Class II flammability requirement per 16 CFR 1610
  - labeling requirements
- SARS-CoV-2 Tests −e.g., molecular
  - Limit of Detection
  - 30 contrived positive & 30 contrived negative clinical specimens (RNA spike in NP swab transport media)
    - 20 at 1x-2x LoD (acceptance 95% agreement)
  - Inclusivity
  - Cross-reactivity
- Place on market within 15 days of EUA request

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Recent Trends

- Next Generation Sequencing
  - Complex submission - analytical and clinical data
  - Test Run Quality Metrics
  - If using Illumina platform - must get license
  - Most submissions De Novo
- Nested Intended Use
  - Tier 1- -Evidence of Clinical Significance
    - CDx for known drugs
  - Tier 2- Potential Clinical Significance
    - Clinical trials, literature sources
  - FDA allows updates to procedure without new submission, new analytes/IU need submission

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Recent Trends (cont.)

- Software Algorithms
  - FDA requires data for all platforms! No agnostic input.
  - Digital Pathology example
    - Scanner, software ingests image- analyze, displays
    - FDA wants clinical validation for all platforms
- Point of Care
  - CLIA Waiver for Simple Tests
    - Microfluidic devices
  - 510(k) for professional point of care use
    - Example emergency ward

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Thank You

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Class II: IVD 510(k) Requirements

- Clinical evaluation: validation of intended use
- Analytical data:
  - Precision/reproducibility
  - Interfering substances
  - Cross reactivity
  - Limit of Detection
  - Stability
  - Linearity, etc.
- Substantial Equivalence: Predicate
- Software validation
- Labeling

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Class II: Monitoring

- Requires multiple time points from same patient (4-6)
- Definition of progression, regression and stable disease
- Comparison to a cleared method (measurement claim)
- Intended Use example: Binding Site [K172613]
  - Optilite Hevylite IgG Kappa is a quantitative in vitro assay performed on the Optilite analyser for the measurement of IgG kappa (IgG heavy chain and kappa light chain intact immunoglobulin) in serum. Measurement of Hevylite Human IgG Kappa is used alongside Hevylite Human IgG Lambda to calculate the IgG Kappa / IgG Lambda ratio. The Hevylite Human IgG Kappa / IgG Lambda ratio can be used when monitoring previously diagnosed IgG multiple myeloma and is used in conjunction with other laboratory tests and clinical evaluations. The assignment of complete response is reliant upon other tests including immunofixation, bone marrow and urine assessments.
  - 284 samples for method comparison
  - 22 patients (69 samples) for monitoring claim

Note: Important to define progression, regression and stable disease

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Class III: Screening

- PMA
- Cologuard: P130017
- Indications for Use
  - *Cologuard* is intended for the qualitative detection of colorectal neoplasia associated DNA markers and for the presence of occult hemoglobin in human stool. A positive result may indicate the presence of colorectal cancer (CRC) or advanced adenoma (AA) and should be followed by diagnostic colonoscopy. *Cologuard* is indicated to screen adults of either sex, 50 years or older, who are at typical average-risk for CRC. *Cologuard* is not a replacement for diagnostic colonoscopy or surveillance colonoscopy in high risk individuals.
  - Trial Design
    - 12,776 patients , 90 sites in US and Canada
    - Stool samples
    - Compared to FIT testing and Colonoscopy

Note: Comparison to clinical outcome

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De Novo

- DEN 170047 Unyvero Lower Respiratory Tract Application
- Intended Use: Detection/ID of 19 organisms & 10 resistance markers
- Benefit/Risk
  - FDA concern that normal flora might contain resistance marker- not necessarily pathogen associated
  - Include limitations in labeling
- Analytical Studies
  - Precision, Repro, LoD, Matrix, In silico, Stability, etc.
- Clinical Validation Study Design
  - Highly Multiplexed Biological/Medical Countermeasure *In Vitro* Nucleic Acid Based Diagnostic Detection Devices
    - https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm327293.htm
  - Prospective cohort – at least 1500 for specificity analysis
  - Retrospective cohort – 50 positive of each analyte
  - Contrived – enhance positive cohort for rare analytes
- Software, Multiple analyte detection, Cybersecurity, etc.

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Single Site 510(k) or De Novo

- Problems
  - FDA quality system requirements differ from CLIA
    - https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/CLIA_Regulations_and_Federal_Register_Documents.html
  - CLIA personnel not familiar with design control, manufacturing requirements
  - Additional regulatory burden for labs
- Benefits
  - Reimbursement
    - [e.g. Foundation Medicine dual FDA/CMS decision]
  - Clinical Utility demonstrated
    - Physician acceptance

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CLIA Waiver: Dual Submission Pathway

- 510(k) –substantial equivalence to predicate
- CLIA Waiver- demonstrate simple and low risk of erroneous result in the hands of an untrained user
- Dual Submission Pathway Study Design
  - https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM586502.pdf
  - Requires pre-submission
  - Decision within 180 FDA days
  - Comparison Study- split sample [minimum of 360 samples]
    - Waived Test
      - At least 3 intended use sites: e.g., clinics, Dr. office
      - At least 9 untrained operators across all sites
    - Comparator Test
      - Trained users on comparator method
    - Total Error calculation
  - Reproducibility Study
  - Operator Questionnaire

Note: Difficult to find sites for split sample Waived/Comparator testing

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Benefit of CLIA Waiver

- If test is categorized as moderate/high complexity
  - market is limited to ~36,000 labs in US
- If test is Waived
  - market is ~126,000 labs in US

Can only sell IVD to lab holding appropriate certificate! Different from other device approvals

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Key "Take Aways" from Recent NGS

- Foundation One CDx- P170019
  - Breakthrough Device Program
  - Genetic mutations in 324 genes & microsatellite and tumor mutational burden in any solid tumor
    - non-small cell lung cancer, melanoma, breast cancer, colorectal cancer or ovarian cancer.
    - Dx for 15 drugs
  - CMS coverage at same time: parallel review program
    - National Coverage Determination (NCD) for Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer
    - Outright coverage when the test is FDA approved and the cancer type has at least one treatment having an FDA approved companion diagnostic.
    - Markers of undetermined significance not covered automatically
  - Unlike most FDA cleared or approved tests, allows for "flexible" approach for additions….see guidance.

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Trends- NGS

- MSK DEN 170080
- Indications for Use:

The MSK-IMPACT assay is a qualitative in vitro diagnostic test that uses targeted next generation sequencing of formalin-fixed paraffin-embedded tumor tissue matched with normal specimens from patients with solid malignant neoplasms to detect tumor gene alterations in a broad multi gene panel. The test is intended to provide information on somatic mutations (point mutations and small insertions and deletions) and microsatellite instability for use by qualified health care professionals in accordance with professional guidelines, and is not conclusive or prescriptive for labeled use of any specific therapeutic product. MSK-IMPACT is a single-site assay performed at Memorial Sloan Kettering Cancer Center.

- 468 genes, single lab

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