Development of Companion Diagnostics – An FDA Perspective

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www.fda.gov
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The views expressed during this presentation are those of the presenter and do not necessarily reflect the policy or position of the US FDA or the US government.

Please visit FDA website for device advice

www.fda.gov
Presentation Topics

• Co-development of drugs and companion diagnostics (CDx)

• Follow-on CDx ("me too")

• Next generation sequencing (NGS)-based oncology panel (oncopanel)

• Liquid biopsy

• Investigational device exemption (IDE)
CDx Opportunities

• Increase in approval of targeted drugs
  – In the early 1990s, 5% of new drug approvals were for targeted therapies
  – In 2013, 45% were for targeted therapies

• Increase in targeted drug development programs
  – Prospectively defined biomarker-positive population
    ➢ Marker-positive: enrolled, safety and efficacy evaluated
  – Prospectively defined retrospective analysis (all comers)
    ➢ All patients enrolled and stratified based on biomarker status
  – Adaptive study design
    ➢ Biomarker-stratified all comers to marker-positives only
Ideal Co-Development Processes

Basic Res.  Preclinical  Clinical

Tractable Hit  Preclinical Evaluation  Investigational New Drug
Lead Candidate  Phase I  Phase II

Biomarker Discovery  Analytical Validation
Assay Prototype

“IDE level” Validation
- For use in Phase I/II exploratory trials
• Does your test measure the analyte you think it does?
• How accurately and reliably does it work in the hands of intended users?

Analytical performance: Sensitivity, accuracy, precision/reproducibility etc
Ideal Co-Development Processes

Basic Res. | Preclinical | Regulatory | Market
---|---|---|---
Tractable Hit | Preclinical Evaluation | Investigational New Drug | NDA
Lead Candidate | | Phase I | BLA
| | Phase II | | Rx
| | Phase III |
Biomarker Discovery | Analytical Validation | Investigational Device | PMA
Assay Prototype | | Exploratory | [510(k)]
| | Clinical Validation | | Dx
FDA 101 on IVD Regulations

Risk-Based Classification of IVDs

- **Class I**: common, low risk devices
  - Most exempt from premarket submission
- **Class II**: moderate risk
  - e.g., prognosis, monitoring in already diagnosed cancer patients
  - Premarket Notification \([510(k)]\)
- **Class III**: complex, high risk or by default
  - e.g., cancer diagnosis or screening, most CDx
  - Premarket Application \([PMA]\)
Regulatory Processes

Class II (moderate risk)

Traditional 510(k)

De novo 510(k)
- No Predicate
- Special Controls
- S&E

FDA Clearance
Device shows substantial equivalence to a legally marketed predicate

Class III (high risk)

Pre-market Approval Application (PMA)

FDA Approval
Device demonstrates safety and effectiveness (S&E)

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Marketing Submissions for CDx

• A PMA submission required for most CDx
• Modular PMA approach highly preferred over traditional
  – CDx review can begin early
  – Final clinical module coincides with BLA/NDA filing
  – CDx review, in practice, follows therapeutic review timeline
• Encourage CDx sponsors to consult CDRH early through pre-submission process
CDx Development Challenges

In reality...

- Business issues
  - Device manufacturers: CDx development, validation, testing, submission, compliance with device regulations
  - Drug manufacturers: Assuring availability of a CDx essential for the safe and effective use of their drug
    - Uncertainty of the CDx needs (e.g., adaptive trials)
    - Underestimate of CDx development efforts
    - Common use of lab developed tests
- Use of one or more clinical trial assays (CTAs) for patient enrollment (partly or completely)
Common Co-Development Processes

Basic Res. | Preclinical | Clinical | Regulatory | Market
---|---|---|---|---
Tractable Hit | Preclinical Evaluation | Investigational New Drug | NDA | Rx
Lead Candidate | | Phase I | BLA |
Biomarker Discovery | Analytical Validation | Investigational Device | | Dx
Assay Prototype | Exploratory | Clinical Trial Assays | | |
Companion Diagnostics Development | Analytical Validation | Bridging Study | PMA (510(k)) |
### Bridging Studies

<table>
<thead>
<tr>
<th></th>
<th>CDx</th>
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<tbody>
<tr>
<td></td>
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<td>Total</td>
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<tr>
<td>CTA</td>
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<td>+</td>
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<td>δ₁</td>
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<td>δ_{CTA+}</td>
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<tr>
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<td>δ₂</td>
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</tr>
<tr>
<td>Total</td>
<td>δ_{CDx+}</td>
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</table>

- Retest CTA+ and CTA- samples by CDx
- Assess agreements between CDx and CTA
- Bridge clinical data from CTA to CDx

\[ δ_{CDx+} = δ₁ \times \Pr(\text{CTA+} | \text{CDx+}) + δ₂ \times [1 - \Pr(\text{CTA+} | \text{CDx+})] \]

Estimation of $\delta_1$ and $\delta_2$

- CTA+ Sample Retesting < 100%
  - Missing or inadequate samples
  - Unstable analytes

- $\delta_1$ estimation: Observed + (Missing data analysis)
  - Robustness under different missing data mechanisms or imputation methods
Estimation of $\delta_1$ and $\delta_2$

- CTA+ Sample Retesting < 100%
  - Missing or inadequate samples
  - Unstable analytes
  - $\delta_1$ estimation: Observed + (Missing data analysis)
    - Robustness under different missing data mechanisms or imputation methods

- $\text{Pr}(\text{CTA+} \mid \text{CDx+}) < 100\%$
  - Inaccuracies and imprecisions of CTA and CDx
  - Different technology/platform or multiple CTAs
  - $\delta_2$ estimate: Sensitivity analysis
Estimation of Pr(CTA+ | CDx+)

- Retesting of CTA+ and CTA- samples by CDx
  - Sufficient retention, but <100%
    - CTA+ Covariate distributions: CDx-evaluables vs CDx-unevaluables
    - CTA- demographics, clinicopathologicals: trial vs re-test population

- External concordance study
  - Insufficient sample retention
    - e.g., CTA- patients not sampled or consented for retesting
    - Representativeness of intended use population
  - Testing of CTA- (and additional CTA+) samples by CDx
  - Testing of CDx+ samples by CTA
    - CDx+ sample cannot be prescreened with CTA
Plan for Bridging Studies

- Use a well-characterized CTA for enrollment in pivotal trial(s) of the therapeutic product
- Ensure informed consent allows retesting
- Archive CTA+ and CTA- patient specimens
  - Annotation (e.g., demographics, clinicopathological info)
  - Re-test population representative of trial population
- Address potential discordance, missing data, biases (selection, spectrum) in statistical analysis plan
- Consult CDRH via pre-submissions early and often
Plan for No Bridging Studies

- Establish biomarker strategy early during drug development program
  - Trial design as determinant of CDx claims
- Use an analytically validated CDx for enrollment
  - A specified specimen type and collection method
  - A defined test platform/technology/regent
  - A validated test protocol
  - A selected clinical decision point (cut-off)
- Comply with Quality System regulations
- Consult CDRH via pre-submissions early and often
Presentation Topics

• Co-development of drugs and companion diagnostics (CDx)

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• Liquid biopsy

• Investigational device exemption
Follow-on CDx – Opportunities

• To date: >20 different approved drug/diagnostic combinations
  – Current list of approved CDx
    www.fda.gov/CompanionDiagnostics

List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools)

A companion diagnostic device can be in vitro diagnostic device or an imaging tool that provides information that is essential for the safe and effective use of a corresponding therapeutic product. The use of an IVD companion diagnostic device with a particular therapeutic product is stipulated in the instructions for use in the labelling of both the diagnostic device and the corresponding therapeutic product, as well as in the labelling of any generic equivalents and biosimilar equivalents of the therapeutic product.

The list of FDA cleared or approved nucleic acid based tests is maintained on a separate page at Nucleic Acid Based Tests.

<table>
<thead>
<tr>
<th>Drug Trade Name (Generic Name)</th>
<th>NDABLA</th>
<th>Device Trade Name</th>
<th>PMA</th>
<th>Device Manufacturer</th>
<th>Intended Use (IU)/Indications for Use (IFU)</th>
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<tr>
<td>imatinib mesylate</td>
<td>NDA 21:335</td>
<td><strong>PDGFRA FISH for Gleevec Eligibility in Myelodysplastic Syndrome/Myeloproliferative Disease (MDS/MPD)</strong></td>
<td>H140005</td>
<td>ARUP Laboratories, Inc.</td>
<td>The PDGFRA FISH for Gleevec Eligibility in Myelodysplastic Syndrome/Myeloproliferative Disease (MDS/MPD)**</td>
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www.fda.gov
## FDA-Approved HER2 CDx

<table>
<thead>
<tr>
<th>Target</th>
<th>Diseases</th>
<th>Therapeutics</th>
<th>Approved CoDx</th>
</tr>
</thead>
</table>
| HER2   | Breast    | Herceptin (trastuzumab)                           | Abbott PATHVYSION HER-2 DNA Probe Kit  
Biogenex InSite Her-2/neu mAb (CB11) kit  
Dako Herceptest  
Dako HER2 CISH pharmDx Kit  
Dako HER2 IQFISH pharmDx  
Leica Bond Oracle HER2 IHC System  
Life Tech SPOT-LIGHT HER2 CISH Kit  
Ventana PATHWAY Anti-HER2 Ab (4B5, CB11)  
Ventana INFORM HER-2/NEU Dual ISH |
| HER2   | Gastric   | Herceptin (trastuzumab)                           | Dako Herceptest  
Dako HER2 IQFISH pharmDx |
| HER2   | Breast    | PERJETA (pertuzumab)  
KADCYLA (ado-trastuzumab emtansine)                | Dako Herceptest  
Dako HER2 IQFISH pharmDx |

**HER2 Follow-on:**  
See published SSED (Summary of Safety and Effectiveness Data) for required studies  
[www.fda.gov](http://www.fda.gov)
# FDA-Approved Non-HER2 CDx

<table>
<thead>
<tr>
<th>Target</th>
<th>Diseases</th>
<th>Therapeutics</th>
<th>Approved CoDx</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF</td>
<td>Melanoma</td>
<td>Mekinist (tramatenib) Tafinlar (dabrafenib)</td>
<td>bioMérieux THxID BRAF kit</td>
</tr>
<tr>
<td>BRAF</td>
<td>Melanoma</td>
<td>Zelboraf (vemurafenib)</td>
<td>Roche COBAS 4800 BRAF V600 Mutation Test</td>
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<tr>
<td>EGFR</td>
<td>NSCLC</td>
<td>GILOTRIF® (afatinib) IRESSA® (gefitinib)</td>
<td>Qiagen therascreen® EGFR RGQ PCR Kit</td>
</tr>
<tr>
<td>EGFR</td>
<td>NSCLC</td>
<td>Tarceva® (erlotinib) Tagrisso® (osimertinib)</td>
<td>Roche cobas® EGFR Mutation Test v2 Roche cobas® EGFR Plasma Test</td>
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<tr>
<td>ALK</td>
<td>NSCLC</td>
<td>XALKORI® (crizotinib)</td>
<td>Abbott VYSIS ALK Break Apart FISH Probe Kit VENTANA ALK (D5F3) CDx Assay</td>
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<tr>
<td>PD-L1</td>
<td>NSCLC</td>
<td>KEYTRUDA® (pembrolizumab)</td>
<td>Dako PD-L1 IHC 22C3 pharmDx</td>
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<td>BRCA1/2</td>
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<td>Lynparza™ (olaparib)</td>
<td>Myriad BRACAnalysis CDx™</td>
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<td>KRAS</td>
<td>CRC</td>
<td>Erbitux® (cetuximab) Vectibix® (panitumumab)</td>
<td>Roche cobas® KRAS Mutation Test Qiagen <em>therascreen</em> KRAS RGQ PCR Kit DAKO EGFR PharmDx Kit</td>
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<td>EGFR</td>
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<td>PDGFRB</td>
<td>MDS/MPD</td>
<td>Gleevec® (imatinib mesylate)</td>
<td>Arup PDGFRB FISH</td>
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<td>KIT</td>
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<td>Arup KIT D816V Mutation Detection</td>
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<tr>
<td>TP53</td>
<td>CLL</td>
<td>VENCLEXTA® (venetoclax)</td>
<td>Abbott VYSIS CLL FISH PROBE KIT</td>
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</tbody>
</table>
Follow-on CDx – Challenges

• No direct estimate of drug efficacy
  – Device not used in original clinical trial
  – Samples from original trial unavailable for retesting
  – Repeat of drug trial impractical or unethical

• Preservation of drug efficacy
  – Effect size
  – Covariates representative of intended use population
  – Analytical sensitivity vs clinical effectiveness
  – Analytical “accuracy” vs clinical effectiveness
Follow-on CDx – Path Forward

• Analytical validation
  – Same gene/variant level validation as original CDx
  – Published SSED as reference

• Method comparison with approved CDx
  – No drug trial required
  – Banked samples from intended use population

• Requirement for preservation of drug efficacy
  – Variability between follow-on CDx and originally approved CDx be within the variability of originally approved CDx

• Consult CDRH via pre-submissions early and often
Presentation Topics

• Co-development of drugs and companion diagnostics (CDx)

• Follow-on CDx (“me too”)

• Next generation sequencing (NGS)-based oncology panel (oncopanel)

• Liquid biopsy

• Investigational device exemption
Next Generation Sequencing (NGS)

• High-throughput sequencing technologies*
  – Roche 454 pyrosequencing
  – Illumina (Solexa) sequencing
  – SOLiD sequencing
  – Ion torrent Proton / PGM sequencing

• Advantages over classical Sanger sequencing
  – Speed – Massively parallel (repeat overlapping reads)
  – Sample Size – Multi-variant/multi-gene in a single assay
  – Sensitivity – Depth of coverage
  – Cost – Time, manpower, reagents

*Not a comprehensive list
Next Generation Sequencing (NGS)

Data analysis

Specimen
DNA
Library
Sequencing
Base calling
Alignment
Variant calling
Annotation / filtering / classification
Interpretation
Report

Fill-in of missing data
orthogonal confirmation

extraction
amplification/capture
NGS-Based Diagnostics – Components

• Library preparation
  – e.g., target primers/capture baits

• Sequencing
  – Instruments, chemistry

• Bioinformatics
  – Sequence alignment (e.g., unmapped reads, haplotype vs diploid)
  – Variant calling (e.g., structural variations)
  – Interpretation (e.g., databases)

• Controls/Reference materials
Potential NGS-Based Applications*

- Noninvasive prenatal testing (NIPT)
- Postnatal germline testing
  - Carrier tests for individuals of reproductive age
  - Whole-genome/whole exome sequencing tests for children with congenital diseases or conditions
  - Whole-genome sequencing tests for individuals to calculate risk of common diseases
- Cancer genetic testing
  - Targeted gene panels
  - Whole-genome/whole exome sequencing tests for patients with end-stage cancers

*Not a comprehensive list
NGS-Based IVDs

• Platform – 21 CFR §862.2265
  – Illumina MiSeqDx instrument (DEN130011; ProCode PFF)
  – ThermoFisher (Life Technologies) Ion PGM™ Dx
  – Vela Diagnostics Sentosa SQ301

• Reagents – 21 CFR §862.3800
  – Illumina Universal reagents (DEN130042; ProCode PFT)
  – ThermoFisher Ion PGM™ Dx Sequencing Kit

• Whole systems – 21 CFR §866.5900
  – MiSeqDx Cystic Fibrosis 139-Variant Assay (K124006)
  – MiSeqDx CF Clinical Sequencing Assay (K132750)
NGS-Based Diagnostics – Challenges

• Applications
  – IVD vs Research Use Only (RUO) platforms

• Components
  – Analyte extraction
  – Library preparation
  – Reference materials/Controls
  – Bioinformatics pipeline
    ➢ Multiple components/steps, Parameters/configurations
    ➢ Algorithms for different variant / specimen types (germline, NIPT)
    ➢ Pipeline validation standards/methodology
    ➢ Benchmarking tools

➤ QC metrics vs system testing
➤ Platform specific vs platform agnostic
Precision Medicine Initiative (PMI) – Modernizing FDA Regulation of NGS Tests

• New regulatory strategies for NGS-based diagnostics
  – Develop and implement **standards** to assure quality
  – Develop **open-source tools** to help test developers meet standards
  – Support the development of **a data commons** for evidence on the clinical relevance of genetic variation

• Goals
  – Develop and implement an adaptive standards-based regulatory approach
  – Enable patient access to their own health information and the software needed for its safe and accurate analysis
FDA Draft Guidance on NGS

• “Use of Standards in FDA Regulatory Oversight of Next Generation Sequencing (NGS)-Based *In Vitro* Diagnostics (IVDs) Used for Diagnosing Germline Diseases”, issued on July 8, 2016

• “Use of Public Human Genetic Variant Databases to Support Clinical Validity for Next Generation Sequencing (NGS)-Based *In Vitro* Diagnostics”, issued on July 8, 2016
FDA Public Workshops on NGS

• Optimizing FDA’s Regulatory Oversight of NGS Diagnostic Tests Public Workshop, Feb. 20, 2015
  – [http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm427296.htm](http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm427296.htm)

• Standards Based Approach to Analytical Performance Evaluation of Next Generation Sequencing In Vitro Diagnostic Tests, Nov. 12, 2015
  – [http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm459449.htm](http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm459449.htm)

• Adapting Regulatory Oversight of Next Generation Sequencing-Based Tests, Sep. 23, 2016
  – [http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm514720.htm](http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm514720.htm)

• Next Generation Sequencing-Based Oncology Panels, Feb. 25, 2016
  – [http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm480046.htm](http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm480046.htm)
NGS-Based Oncology Panel

- Multi-variants/multi-genes in a single oncopanel
  - Unprecedented ability to detect rare and novel variants
- Rapidly evolving technology
  - Whole genome, exome, targeted-sequencing, RNA-Seq, methylation sequencing
  - High throughput, complex, evolving, big data, software standardization, etc
- Sensitivity, accuracy, throughout, reduced cost
  - Increasingly employed in the clinical setting
  - Solution to limited sample availability
Oncopanel Validation Challenges

• Analytical Validation
  – Multiple genes/variants/variant types (SNVs/indels/CNVs/fusions/undefined/novel variants)
  – Multiple analyte types (DNA, RNA, methylation)
  – Multiple specimen types (Blood, FFPE)
  – Germline vs. somatic
  – Comparator methods and reference materials
  – Big data, software standardization

• Clinical Validation
  – Single test, multiple biomarkers, multiple indications
Oncopanel Validation – Path Forward

• Analytical Validation
  – Established QC metrics at each step of the NGS processes
  – Representative subsets of variants covering the range of variant types, sizes and genomic regions/contexts
  – Well-validated orthogonal methods for accuracy study
  – Representative/difficult and challenging tumor types (e.g., bone, brain, pancreas, thyroid) for ‘pan-cancer’ claim

• Clinical Validation
  – Prospective trial for CDx
  – Method comparison study for follow-on CDx claim

• Consult CDRH via pre-submissions early and often
Presentation Topics

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- Follow-on CDx (“me too”)
- Next generation sequencing (NGS)-based oncology panel (oncopanel)
- Liquid biopsy
- Investigational device exemption
Liquid Biopsy – Opportunities

• Genetic testing
  – Non-invasive cfDNA/ctDNA

• Cancer screening
  – Epi Procolon: niche population

• Companion diagnostics
  – cobas EGFR Plasma Test

• Disease monitoring
  – Mutation load detection
  – Drug responses
  – Recurrence/MRD

FDA News Release

FDA approves first blood test to detect gene mutation associated with non-small cell lung cancer

For Immediate Release
June 1, 2016

Release

The U.S. Food and Drug Administration today approved the cobas EGFR Mutation Test v2, a blood-based companion diagnostic for the cancer drug Tarceva (erlotinib). This is the first FDA-approved, blood-based genetic test that can detect epidermal growth factor receptor (EGFR) gene mutations in non-small cell lung cancer patients. Such mutations are present in approximately 10-20 percent of non-small cell lung cancers (NSCLC).

Lung cancer is the leading cause of cancer-related death among men and women in the U.S. and, though more common in men, the number of deaths from lung cancer in women is increasing. According to the National Cancer Institute, an estimated 221,200 Americans will be diagnosed with lung cancer, and 158,040 will die from the disease this year. NSCLC is the most common type of lung cancer. NSCLC tumors may shed tumor DNA into a patient’s blood, making it possible to detect specific mutations in blood samples. Testing for tumor DNA using a blood sample is also called a “liquid biopsy.”

“Approvals of liquid biopsy tests make it possible to deliver highly individualized health care for patients,” said Alberto Gutierrez, Ph.D., director of the Office of In Vitro Diagnostics and Radiological Health in the FDA’s Center for Devices and Radiological Health. “Liquid biopsies also have the potential to allow physicians to identify patients whose tumors have specific mutations in the least invasive way possible.”

www.fda.gov
Liquid Biopsy – Challenges

• Preanalytical
  – Analyte stability and sample process control

• Analytical sensitivity and specificity

• Biological variability/Tissue heterogeneity
  – Tumor type/stage, meds
  – Temporal, spatial

• Clinical
  – Follow-on claim
  – Use with conjunctive tests?

• Consult CDRH via pre-submissions early and often

FDA News Release

FDA approves first blood test to detect gene mutation associated with non-small cell lung cancer

However, if such mutations are not detected in the blood, then a tumor biopsy should be performed to determine if the NSCLC mutations are present. Insofar as the test provides positive results, it may benefit patients who may be too ill or are otherwise unable to provide a tumor specimen for EGFR testing.
Presentation Topics

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• Investigational device exemption
Investigational Device Exemption

- Legal basis for shipping an otherwise illegal device in interstate commerce
  - Collect data to support pre-market submission/publication

- "For Investigational Use Only (IUO)" Labeling
  - "CAUTION - Investigational device. Limited by Federal (or United States) law to investigational use."

- IRB review and Informed consent

- IDE submission to, and approval by, FDA is required
  - IF device has potential of significant risks to patients
Study Risk Determination for CDx

• Submission and approval of an IDE required if
  – The device is used to select patients for enrollment AND
  – The study is considered significant risk study because:
    ➢ Patients will forgo other alternative therapies that are approved or otherwise considered effective
    ➢ Patients may experience investigational drug-associated toxicities that are considered unacceptable
    ➢ Patients who will be enrolled due to incorrect test results may have detrimental effects based on a priori knowledge
    ➢ Patients will undergo invasive procedure solely for testing purpose

• IRBs can and do make risk assessment
• FDA makes final risk determination via SRD pre-subs
IDE Requirements*

- Fully specified device with sufficient analytical validation and clinical information
- Pre-specified investigational plan
  - Study sites (enrollment sites, testing sites)
  - Investigator list and qualifications
  - Number of subjects (to be tested and enrolled)
  - Sampling and test plans (e.g., SOPs)
- Informed consent
- Regular progress reports
- Study can start if no FDA decision on IDE by Day 30

*Not a comprehensive list
All Device Investigations

Studies Subject to IDE Reg.

If the testing:
- Is non-invasive
- Does not require an SR invasive sampling procedure
- Does not by design or intention introduce energy into a subject
- Is not used as a diagnostic procedure without confirmation by another medically established diagnostic product or procedure

Studies Exempt from IDE Reg.
All Device Investigations

Studies Subject to IDE Reg.

- Significant Risk
  - Full IDE Requirements

- Non-Significant Risk
  - Abbreviated Requirements

Studies Exempt from IDE Reg.
Take Home Message

• Plan for co-development
  – Trial design as determinant of CDx claim
  – Biomarker strategy to identify CDx need and partner early
  – IDE submission to, and approval by, FDA before trial starts

• What is on the horizon
  – NGS-based diagnostics (e.g., Oncopanel)
  – CDx follow-on (“me too”)
  – Liquid biopsy – cfDNA/ctDNA

• Consult CDRH via pre-submissions early and often
Thank you!

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Backup slides
What You See as Medical Device

• Specimens
  – Whole blood/plasma
  – Buccal swab
  – Tumor Tissue
  – Urine/Fecal

• Methodologies
  – PCR/dPCR
  – FISH
  – Microarrays
  – NGS

• Analytes
  – DNA (including methylated DNA)
  – RNA
  – Proteins

• Outputs
  – Qualitative (e.g., SNP, mutation status)
  – Quantitative (e.g., copy number, transcript level)
  – Gene Signatures “score”
What FDA Reviews in Medical Device

• Sample Collection
  – Whole blood/plasma
  – Buccal swab
  – Tumor Tissue
  – Urine/Fecal

• Analyte Extraction
  – DNA (including methylated DNA)
  – RNA
  – Proteins

• Instrumentation
  – PCR/dPCR
  – FISH
  – Microarrays
  – NGS

• Software
  – Qualitative (e.g., SNP, mutation status)
  – Quantitative (e.g., copy number, transcript level)
  – Gene Signatures “score”
Device Classification

21 CFR Parts 862-892

• Classifications and descriptions
  – ~1,700 types of devices
  – 16 categories of medical specialties (panels)

• Risk-based on classification
  – The risk of an IVD is based on the consequences of a false result
  – Intended use / Indications for use
  – Three classes: Class I, Class II, or Class III
Class I: Common, Low Risk Devices

- Subject to General Controls
  - Prohibition against adulteration and misbranding
  - Registration and Listing
  - Quality System Regulation (GMPs)
  - MDR Reporting / Reports of Corrections and Remova1s

- General controls known to be sufficient to provide reasonable assurance of the safety and effectiveness

- Or not intended to support or sustain human life or prevent impairment of human health, and without a potential unreasonable risk of illness or injury

- Most exempt from premarket submission
Class II: Moderate Risk Device

• Cannot be Class I

• Sufficient information to establish Special Controls
  – Promulgation of performance standards
  – Postmarket surveillance / Patient registries
  – Development and dissemination of guidelines
  – Recommendations, and other appropriate actions
  – For a device intended “for a use in supporting or sustaining human life, the Secretary shall examine and identify the special controls, if any, that are necessary to provide adequate assurance of safety and effectiveness and describe how such controls provide such assurance”

• Premarket Notification [510(k)]
Class III: High Risk (or by default)

- Cannot be Class I
  - Insufficient information exists to determine that the application of general controls are sufficient to provide reasonable assurance of the safety and effectiveness, and

- Cannot be Class II
  - Insufficient information exists to determine that the special controls would provide reasonable assurance of its safety and effectiveness, and

- Intended support or sustain human life or prevent impairment of human health, or presents a potential unreasonable risk of illness or injury

- Premarket Application [PMA]