In vitro Device Regulation

David W Feigal, M.D., M.P.H.
Genetically Guided Diagnostics

Who are the Test Developers?

- Molecular Pathologists
- Reagent (Analyte) Manufacturers
- High Complexity Clinical Labs
  - Commercial
  - Academic
- In Vitro Diagnostics Manufacturers
- Drug Developers – large & small
Oversight of In Vitro Diagnostics

States

Center for Devices and Radiological Health

Medical Devices

Health Professionals

IRB’s

Health Facilities

Clinical Laboratories Improvement Amendments (CLIA) Program
In Vitro Diagnostics

The Oversight Groups

- Physician peer review
- IRBs
- College of American Pathologists
- CMS
- State health professional licensing
- FDA (CDRH, CDER, CBER)
- Regulatory Bodies outside US
- Purchasers
Diagnostic Device Life-Cycle
Diagnostic Device Life-Cycle

Reagent Manufacturer
In House Tests – “Home Brew”

- Established practice
- Long history
- Regulated by CLIA
- *Use FDA approved devices and reagents*

**Analyte Specific Reagents**

- Building blocks or active ingredients of in house tests
- Designed to allow for in house tests under incremental control
- Classification – usually Device class 1 exempt always classified as CLIA high complexity
**ASR Rule  (Analyte Specific Reagents)**

**Manufacturer Responsibilities**
- Manufacturers must register and list, follow Quality System Regulations (QSRs)
- Sales restricted to high complexity labs
- Labs must establish performance and label accordingly
- Most ASRs are exempt from FDA pre-market review
- MDR Reporting (adverse experiences) to FDA required

**Lab Responsibilities**
- High complexity labs
- Establish performance
- Test Labeled as in house test
- Mandatory labeling
- Discretionary labeling
Diagnostic Device Life-Cycle

- Quality System
- Design Controls
- CAPA: Corrective and Preventive Actions
- MDR Reporting

Informed Consent
IRB oversight
Protocol

IVD Equipment and Kit Manufacturers
Diagnostic Device Life-Cycle

Class I: No review
Class II: 510(k)
Class III: PMA

MDR Reporting
Recalls
Labeling Revisions
Regulation of *in Vitro* Diagnostics

**Authorities:**

*Food Drug and Cosmetic Act*

- **Device Amendments**
  - Food and Drug Administration
    - Center for Devices and Radiological Health (CDRH)
    - Center for Biologics Evaluation and Research (CBER)

*Public Health Services Act*

- **Clinical Laboratories Improvement Act**
  - Center for Medicare and Medicaid Services (CMS)
    - Laboratory Certification
  - Food and Drug Administration
    - In Vitro diagnostics CLIA complexity classification
FDA Authority

FDA Definition of a Device

- Instrument, apparatus, implement, machine, contrivance, implant, *in Vitro* reagent, or other similar or related article, including any component, part, or accessory, which is:
  - 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, or
  - intended to affect the structure or any function of the body of man or other animals,

and …
FDA Authority

FDA Definition of a Devices

… and,

which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.
CLIA Authorities

“Laboratory” or “clinical laboratory” defined

As used in this section, the term “laboratory” or “clinical laboratory” means a facility for the biological, microbiological, serological, chemical, immuno-hematological, hematological, biophysical, cytological, pathological, or other examination of materials derived from the human body for the purpose of providing information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings.
CLIA Authorities

Certificate requirement

No person may solicit or accept materials derived from the human body for laboratory examination or other procedure unless there is in effect for the laboratory a certificate issued by the Secretary (of HHS) under this section applicable to the category of examinations or procedures which includes such examination or procedure.

Note that even diagnostics done under IDE and labeled, as required by FDA, “for research use only” must be performed in a CLIA certified laboratory if the patient or doctor gets the results.
Regulatory Authorities

FDA
- Laboratory “Things”:
  - Specimen collection devices
  - Reagents
  - Instruments

CMS – CLIA
- Laboratory Processes and Personnel
  - Specimen preparation processes
  - Clinical Pathology Interpretation
  - Use of “Things” (SOPs, proficiency etc….)
FDA Risk Classification

Risk Assessed on Claim and Use

- **Class 1**
  - Most exempt from pre-market notification

- **Class 2**
  - 510(k) notification

- **Class 3**
  - Pre-market Application (PMA)
Advantages of a 510(k) over PMA

Even when a 510(k) requires clinical trials …

- 510(k) applications are very streamlined
- They are approved on average in 90 days vs. 400 days
- There are no annual or periodic reports
- There are no product supplements
- Labeling changes may be done without prior approval
- Manufacturing changes may be done without prior approval
CLIA Complexity Classification

Assessed on Complexity of the Process

- **Waived tests**
  - Are cleared by the Food and Drug Administration (FDA) for home use;
  - Employ methodologies that are so simple and accurate as to render the likelihood of erroneous results negligible; or
  - Pose no reasonable risk of harm to the patient if the test is performed incorrectly.

- **Moderate Complexity**
  - Including provider performed microscopy

- **High Complexity**
CLIA Complexity Classification

Assessed on Complexity of the Process

- Waived tests
  - Point of Care
- Moderate Complexity
  - Doctors Office
- High Complexity
  - Clinical Laboratory
# Oversight Requirements

<table>
<thead>
<tr>
<th></th>
<th>MD</th>
<th>Lab</th>
<th>ASR Manufacturer</th>
<th>IVD</th>
<th>Drug Developer</th>
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<tbody>
<tr>
<td></td>
<td>CLIA</td>
<td>FDA</td>
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<tr>
<td>Informed Consent</td>
<td>+/-</td>
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<td>+/-/-</td>
<td>++/</td>
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<tr>
<td>GMP Manufacturing</td>
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<td>++</td>
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<td>Recalls</td>
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<tr>
<td>Analytic Reproducibility</td>
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<tr>
<td>Safe and Effective Claim</td>
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</table>
Regulation & RNA based Diagnostic

Collection

Extraction

Amplification

Analyte Measurement

System

RNA Collection Devices Class II

General Purpose Reagents (Class I)

PCR / Gene Chip – Class II

Matrix Index Assay – Class II or III

Interpretation
The device may consist of:
- sample collection devices,
- nucleic acid isolation and purification reagents, and
- processing reagents/equipment (tubes, columns, etc.).

It also may contain:
- instruments for automation of the nucleic acid isolation and purification steps.
Class II RNA Preanalytical Systems

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  - nucleic acid isolation and purification reagents, and
  - processing reagents/equipment (tubes, columns, etc.).

- It also may contain
  - instruments for automation of the nucleic acid isolation and purification steps.

It also may contain instruments for automation of the nucleic acid isolation and purification steps.
FDA Guidance: RNA Collection

**Guidance Sections:**
- Device Description
- Intended Use
- Performance Characteristics
  - Collection parameters
  - RNA Quality assessment
    (yield, stability, purity, suitability for PCR)
  - Device Stability and Precision
- Instrumentation and software
- Proposed Labeling
  - Directions for Use / User Manual
Regulation & RNA Diagnostic

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Interpretation
FDA Guidance: ASR Rule

Analyte Specific Reagent Rule

- Final Nov 1977
- Created a regulatory path for Reagent manufacturers
- Most ASR’s Class I exempt
- ASR’s used in “home brew” and FDA approved IVD’s
Antibodies, specific receptor proteins, nucleic acid sequences, and similar biological reagents which through chemical binding or reaction with substances in specimen are intended for identification and quantification of an individual chemical substance or ligand in biological specimens

i.e., the “active ingredient” of an IVD
ASRs in Home Brew Use

- Individual ligand
- Laboratory assembles using general purpose reagents and equipment
- Laboratory develops protocol
- Laboratory validates, labels and markets for specific clinical indications
- Laboratory troubleshoots
Regulation & RNA Diagnostic

Collection
Extraction
Amplification
Analyte Measurement
System

RNA Collection
Devices Class II

General Purpose Reagents
(Class I)

PCR / Gene Chip – Class II

Matrix Index Assay
– Class II or III

Interpretation
FDA Guidance IVD Matrix Index Assays

IVDMIA is a test system that employs data, derived in part from one or more in vitro assays, and an algorithm that usually, but not necessarily, runs on software, to generate a result that diagnoses a disease or condition or is used in the cure, mitigation, treatment, or prevention of disease.
IVDMIs reflect the following characteristics:

1. Use clinical data -- including data from one or more in vitro assays and, in some cases, demographic data -- to empirically identify variables and to derive weights or coefficients employed in an algorithm;

2. Employ the algorithm to integrate these variables in order to calculate a patient-specific result (e.g., a “classification,” “score,” or “index”). This result cannot be independently derived and confirmed by another laboratory without access to the proprietary information used in the development and derivation of the test; and

3. Report this result, which cannot be interpreted by the well-trained health care practitioner using prior knowledge of medicine without information from the test developer regarding its clinical performance and effectiveness.
Regulation & RNA Diagnostics

Collection

Extraction

Amplification

Analyte Measurement

Interpretation

RNA Collection Devices Class II

General Purpose Reagents (Class I)

PCR / Gene Chip – Class II

Matrix Index Assay – Class II or III
Put it all together and …

…what have you got?

A Claim

- Claims require evidence
- Evidence determines your claim
### Claims

<table>
<thead>
<tr>
<th>General</th>
<th>“RNA collection device”</th>
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</thead>
<tbody>
<tr>
<td>Specific</td>
<td></td>
</tr>
<tr>
<td>Analytic</td>
<td>“Her 2 Neu”</td>
</tr>
<tr>
<td>Diagnostic</td>
<td>“Cystic Fibrosis”</td>
</tr>
<tr>
<td>Predictive</td>
<td>“At risk for breast cancer”</td>
</tr>
<tr>
<td>Prognostic</td>
<td>“Aggressive breast cancer”</td>
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## Business Model

<table>
<thead>
<tr>
<th>Component Manufacturer</th>
<th>Responsibility of the Finished Device Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finished Device Manufacturer</td>
<td>Registers the Company Lists the Products Gets FDA clearance / approval</td>
</tr>
<tr>
<td>Accessory Manufacturer</td>
<td>A type of finished device that is used with another approved device</td>
</tr>
<tr>
<td>Kit Assembler (of FDA approved Devices)</td>
<td>Registers the Company Lists the Products</td>
</tr>
</tbody>
</table>
Business Models:

RNA Collection
Devices Class II

Sales to Health Care Providers

FDA Class II Application for Collection Device

<table>
<thead>
<tr>
<th>Pro</th>
<th>Con</th>
</tr>
</thead>
</table>
| ☑ Based on RNA collection without any specific Claim  
   ☑ Device approved for any collection use | ☑ Possible follow-on products  
   ☑ Not a ‘premium product’ |
Regulation & RNA based Tests

Extraction
Amplification
Analyte Measurement

General Purpose Reagents (Class I)

PCR / Gene Chip – Class II

Provide in a Reference Laboratory as Home Brew

Purchase for Home Brew Use

Pro
- Could launch diagnostic from a Reference Lab
- No FDA oversight on the claim associated with the device
- FDA approved reagents for extraction & amplification

Con
- No FDA approved Gene Chip
- FDA likely not to view the test as home brew unless using individual reagent PCR
Regulation & RNA based Tests

General Purpose Reagents (Class I)

PCR / Gene Chip – Class II

Sell a medical device to CLIA High Complexity labs

FDA Class II or Class III approval based on Claim

Pro

- Diagnostic sales to CLIA Laboratories
- A proprietary gene chip could protect IP
- FDA approved reagents for extraction & amplification could be provided by Labs

Con

- FDA regulation would take longer than CLIA route
- Some CLIA labs might try to “knock off” your system with their own home brew
## Regulation & RNA based Tests

### Interpretation

<table>
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</thead>
<tbody>
<tr>
<td>With FDA approval could sell test results from either a reference lab or as part of diagnostic system to a CLIA High Complexity Lab</td>
<td>Different claims would require separate FDA clearance or approval</td>
</tr>
</tbody>
</table>

### Matrix Index Assay – Class II or III

- Sell diagnostic information to Health Care Providers from a Reference Lab
- Sell as medical device to CLIA High Complexity labs

**FDA Class II or Class III Matrix Index Array**
Case Study: Immuneon

Regulatory Approvals

- All 510(k) approvals
- Separate approvals for different system components

IMMUNEON CELLTRACKS ANALYZER IMMUNEON CORP. K030263 GKH ... more
IMMUNEON CELLSAVE PRESERVATIVE TUBE IMMUNEON CORP. K030596 JKA ... more
IMMUNEON CELLTRACKS AUTOPREP SYSTEM IMMUNEON CORP. K040077 GKH ... more
CELLTRACKS ANALYZER II IMMUNEON CORP. K060110 NQI ... more
CELLTRACKA ANALYZER II IMMUNEON CORP. K050145 NQI ... more
CELLPREP SAMPLE PREPARATION SYSTEM, MODEL 9518 IMMUNEON CORP. K022512 GKH ... more
Case Study: Immunicon

Overview of Products and Services

Immunicon has developed a portfolio of products to capture, count and characterize circulating tumor cells (CTCs). The CellTracks AutoPrep System is a one-step automated platform designed to isolate, capture, and identify CTCs from whole blood. The CellTracks AutoPrep System is used to isolate CTCs from whole blood and perform molecular analysis on the isolated cells. Immunicon also offers a suite of services to incorporate rare cell analysis into your programs.

Products for Rare Cell Analysis

- CellTracks™ AutoPrep System
- CellTracks™ Analyzer II
- Kits & Marker Reagents
- CellTracks™ Preservation Tube
- Pharma Services

Pharma Services

Immunicon collaborates with pharmaceutical and biotechnology companies on assays and offers rare cell testing services to incorporate rare cell analysis into your programs.

Prevalence of CTCs at Baseline

CTC vs. Survival for 177 Metastatic Breast Cancer Patients

- The X-axis shows the number of CTCs per 10 ml of whole blood.
- The Y-axis shows the survival of patients with CTCs in their blood.
- The figure shows that patients with higher CTC counts have lower survival rates.
- The median survival time for patients with CTCs in their blood is significantly lower than for CTC-negative patients.

Survival Analysis using ≤5 CTC Threshold

Overall Survival Analysis Using Baseline CTC Values

- Patients with ≤5 CTCs at baseline had a longer overall survival compared to patients with more than 5 CTCs.
- The median survival time for CTC-negative patients was significantly longer than for CTC-positive patients.
- In multivariate analyses that included clinical and pathological factors, CTC count was the strongest predictor of survival.


10/7/2006
What Business do you want to be in?

Device component manufacturer
- You design the product

Contract Manufacturer
- Your customer designs the product

Finished Device Manufacturer
- You deal with FDA

Kit Assembler
- Your suppliers have already dealt with FDA

Reference Lab with an in house test
- You deal with CLIA

Device manufacturer with sales to Labs and POC
- You deal with FDA and CLIA complexity classification

Soothsayer
- Give up on making devices and become a consultant