Submission of a companion diagnostic test to the FDA for detection of KIT D816V mutations in aggressive systemic mastocytosis.

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Dr. Kelley declares affiliation with Novartis (Advisory Board, Consultant).

Outline

• Perspective of practicing pathologist (not a regulatory expert)
• Systemic mastocytosis and imatinib
• Companion diagnostic devices
• Test submission to the FDA
• Quality systems and design control
• Test validation and deployment
• Summary
  • Lessons learned
  • No position for or against regulation of LDTs

Recent events – FDA guidance

• September 30, 2014: FDA releases draft guidance outlining intent to enforce regulation of laboratory developed tests (LDTs)
  • FDA aims to require more robust analytical validity (vs CLIA) as well as clinical validity
  • FDA has exercised enforcement discretion over LDTs
  • Guidance raises controversial and subject of much debate from stakeholders
  • Issues raised:
    • Necessity
    • Authority
    • Feasibility
    • Impact on innovation
• November 18, 2016: FDA announces indefinite delay in finalization of guidance related to LDT regulation
• Much uncertainty exists
Systemic Mastocytosis

- SM: caused by accumulation of neoplastic mast cells in bone marrow and other organs
- Mast cells are morphologically and immunophenotypically abnormal
- Activating mutations in KIT (KIT D816V)
- Incurable – therapy for management of symptoms
- Rare disease with estimated annual incidence: 5-10 cases per million population
- Symptoms related to release of mast cell mediators: histamine, cytokines, proteases, serotonin, etc

Mastocytosis – 2016 WHO

- Diagnostic criteria (1 major and 1 minor or 3 minor)
  - Major: multifocal dense aggregates of mast cells (>15) in bone marrow and other extracutaneous organs
  - Minor: atypical morphology (>25%), aberrant immunophenotype, Detection of KIT codon 816 mutation; increased serum tryptase (>20ng/mL)

Systemic Mastocytosis

- KIT
  - Receptor protein tyrosine kinase
  - Located at 4q12
  - Ligand is stem cell factor
  - Children – extracellular domain mutations
  - Adults – tyrosine kinase domain mutations @codon 816: D816V, D816Y, D816H

KIT mutations in mastocytosis

- Potential detection methods
  1. Sanger sequencing: little to no utility in mastocytosis patients due to poor sensitivity
  2. Next generation sequencing (NGS) panels: Slightly better sensitivity; potential detection of other associated mutations (TET2, SRSF2, ASXL1, etc)
  3. Allele specific PCR: much better sensitivity but limited to KIT D816V

Treatment of mastocytosis

- Symptomatic treatment
  - Antihistamines
  - Corticosteroids
  - Cytoreductive agents
  - 2CDa
  - Interferon-alpha
  - Hydroxyurea
  - Imatinib – for KIT D816V negative patients
    - KIT D816V mutation dysregulates receptor conformation leading to a constitutive active state
    - Imatinib cannot bind to activated KIT
- Clinical trials
  - Novel TKIs not approved for this indication – midostaurin, masitinib, etc
  - AHD
  - Treated separately from SM, as appropriate
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**Imatinib and ASM**

*From: Alvarez-Twose et al. Oncotarget, 2016*

**Response of 4 patients lacking KIT D816V to imatinib**

*In general, the literature demonstrates a better imatinib response rate for patients with ASM lacking KIT D816V mutations.*

**Serum tryptase**

%BM mast cells

*From: Alvarez-Twose et al. Oncotarget, 2016*

**Before**

Skin bx; Tryptase stain

BM bx; CD117 stain

**After 12 mos imatinib**

**Gleevec (imatinib) Rare Diseases Program**

*Novartis made a post-market commitment to FDA to provide for companion diagnostic tests for Gleevec rare diseases including aggressive systemic mastocytosis (ASM)*

*Novartis contracted with ARUP to develop, verify and validate a CDx assays for KIT D816V for ASM, to be offered at ARUP labs*

*PDGFRB FISH assay was also the subject of a similar program for determination of imatinib eligibility but will not be discussed here.*

*We re-developed our existing KIT D816V assay in accordance with 21 CFR 820 (quality systems regulation for medical devices) using a new product development program*

*We received FDA approval under the HDE pathway*

**KIT D816V Mutation Detection by PCR for Gleevec Eligibility in Aggressive Systemic Mastocytosis (ASM)**

**Companion and Supportive Diagnostic Tests**

*Imatinib (Gleevec) – Indications for use: Adult patients with aggressive systemic mastocytosis without the KIT D816V mutation or with KIT mutation status unknown*

*small subset of patients are eligible in context of a rare disease*

**In vitro Companion Diagnostic Devices**

*Definition: An IVD could be essential for the safe and effective use of a corresponding therapeutic to:*

*• Identify pts who are most likely to benefit from the therapeutic product*

*• Identify pts likely to be at increased risk for serious adverse reactions as a result of treatment with the therapeutic product*

*• Monitor response to treatment with the therapeutic product for the purpose of adjusting treatment to achieve improved safety or effectiveness*

*• Identify pts in the population for whom the therapeutic product has been adequately studied, and found safe and effective*

**Approval Pathways**

*De novo*

*No predicate device*

*Class 1 or Class 2*

*Premarket approval (PMA) – classic pathway*

*HDE – "abbreviated" PMA; no clinical studies required*

*510(k) - predicate PMA exists*

*Applying new or expanded knowledge*

Predicate device – marketed device which is substantially equivalent to proposed device. FDA decides what constitutes a substantially equivalent device.

**Humanitarian Device Exemption**

*Humanitarian Use Device (HUD) - a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in <4,000 individuals in the United States per year (recently changed to <8,000 individuals per year)*

*Similar in form and content to a premarket approval (PMA)*

*Exempt from effectiveness requirements*

*Not required to contain results of clinical investigations demonstrating the device is effective for its intended purpose*

*Device may not pose an unreasonable or significant risk of illness/injury*

*Probable benefit to health outweighs risk of illness/injury*

*No comparable (FDA-approved) devices are available*

*Single site approval; at institution with a local IRB to supervise clinical testing*

*Pre-market inspection may not be required*
Submission of a companion diagnostic test to the FDA for detection of KIT D816V mutations in aggressive systemic mastocytosis.

**Original assay:**
- Developed according to CLIA/CAP guidelines and was first clinically available in February 2007.
- Agarose gel-based detection of PCR products.

**HDE assay:**
- 4 years start to finish.
- Limited to fresh bone marrow specimen only (EDTA).
- Allele-specific PCR, capillary electrophoresis detection.

- ~80% of ASM patients have the mutation and are NOT eligible for Gleevec.

**Intended Use (test website, ordering information):**

- KIT D816V Mutation Detection by PCR for Gleevec Eligibility in Aggressive Systemic Mastocytosis (referred to as the "KIT D816V assay") is an in vitro diagnostic test intended for qualitative polymerase chain reaction (PCR) detection of KIT D816V mutational status from fresh bone marrow samples of patients with aggressive systemic mastocytosis. The KIT D816V mutational assay is indicated as an aid in the selection of ASM patients for whom Gleevec® (imatinib mesylate) treatment is being considered. This assay is for professional use only and is to be performed at a single laboratory site.

**Background on the KIT D816V Assay**

**A** | **B** | **B**
---|---|---
No template | Neg control | Pos control

2 PCR reactions

**Example data – Detection by capillary electrophoresis**

- Wild type peak – 182 bp
- Mutant peak – 85 bp

Positive for Kit D816V

**Developing a design control program in accordance with 21 CFR part 820 Quality System Regulations for Medical Devices**

**Quality management system**

- We adhere to the quality system requirements and standards under CLIA, CAP and the various individual states in which we operate.
- In order to achieve FDA approval of the Gleevec companion diagnostics under the HDE program, we implemented a new design control program for developing, validating, and manufacturing the specific approved laboratory assays within our existing quality management system.
- The design control program is maintained by our corporate compliance department.
- Our experience with this project was a key factor in allowing us to upgrade our overall laboratory quality system to meet the requirements of ISO 15189.
  - International Organization for Standardization
  - Specifies requirements for quality and competence of medical laboratories.
Quality System Augmentation

Each applicable element of the FDA QSR was mapped to an existing ARUP policy/procedure. Documents were organized for easy accessibility and retrieval.

The gaps are closed:
- Complaint handling/medical device reporting
- Design Control
- Document controls
- Purchasing controls

- We have processes for handling complaints (communication and documentation)
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- We have policies that can meet the requirements for length of time documents should be stored and readily accessible (master control).

Well defined system to handle (complaint – reportable or not?)

- We have processes for handling complaints (communication and documentation)
- We have policies that can meet the requirements for length of time documents should be stored and readily accessible (master control).

We developed the systems and processes necessary to fulfill the requirements of the FDA for a single site companion diagnostic test approval through the HDE pathway.

The process was lengthy and expensive, even for a relatively simple assay, but provided valuable experience.

We developed a formal system to guide and document test development (not formally documented under CLIA/CAP).

확정된 사항 및 표준 사항 등, ex. primers - who do we buy from, what type of tube/container, QC, certificate

• Procedures to select and approve suppliers including monitoring program to select and approve suppliers including monitoring

Documents were organized for easy accessibility and retrieval.

We developed a formal policy to identify/qualify/monitor vendors of critical components, define and formalize component specifications (ex. primers).

• We have processes for handling complaints (communication and documentation)
- We have policies that can meet the requirements for length of time documents should be stored and readily accessible (master control).

Validation experiments require large numbers of samples, such as:
- Surrogate specimens
- Residual archived extracted DNA
- Interference testing

Overview of Interactions with FDA

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
</tr>
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<tbody>
<tr>
<td>July 26, 2012</td>
<td>Pre-IDE meeting with CDRH/OIVD</td>
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<tr>
<td>September 30, 2014</td>
<td>Qualify/manufacturing modules submitted</td>
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<tr>
<td>November 26, 2014</td>
<td>Analytical/software modules submitted</td>
</tr>
<tr>
<td>December 18, 2015</td>
<td>HDE assays approved by FDA</td>
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<tr>
<td>January 19, 2016</td>
<td>KIT D816V assay launched</td>
</tr>
<tr>
<td>February 16, 2016</td>
<td>PDGFRB FISH assay launched</td>
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Surrogate Specimens and archived samples

- Validation experiments require large numbers of samples, such as:
  - Surrogate specimens
  - Residual archived extracted DNA
  - Interference testing

Experiments performed in the R&D setting:
- Analytical sensitivity
- Analytical specificity
- Limit of detection
- Linearity
- Concordance with alternative lab method/clinical diagnosis

- Surrogate Specimens and archived samples
  - Surrogate specimens – normal bone marrow from donor (commercially sourced) mixed with cell line containing KIT D816V mutation
  - Residual archived extracted DNA
  - Interference testing

For KIT D816V allele-specific PCR test, contrived samples and residual DNAs were heavily used.

- Surrogate specimens – normal bone marrow from donor (commercially sourced) mixed with cell line containing KIT D816V mutation
- Residual archived extracted DNA
- Interference testing

Conclusions

- We developed the systems and processes necessary to fulfill the requirements of the FDA for a single site companion diagnostic test approval through the HDE pathway.
- The process was lengthy and expensive, even for a relatively simple assay, but provided valuable experience.
- Without exception our interactions with the FDA were positive and characterized by openness, professionalism, collegiality and responsiveness.
- Experience gained helped us in acquisition of ISO 15189 accreditation
- Approval for a single site companion diagnostic test is achievable in an academic/reference lab environment.
Acknowledgements

- ARUP Pharma Dx team
  - Karen Heichman, PhD (VP, Director Pharma Dx program)
  - Jorja Warren (Assay Development, Project Manager)
  - Toni Pollock (Software Validation)
  - Alexandra Merkle (Regulatory Project Manager)
- ARUP Executive Team
  - Sherré Perkins, MD, PhD (Senior Vice President, Chief of Clinical Pathology, Director of R&D)
- ARUP Molecular Oncology Laboratory
  - Dan Anderson, MT (Technical Supervisor)
  - Patty Miller (Group Manager)

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No claims can be processed after that date!

After September 30, 2017 you will NOT be able to obtain any CME or SAMs credits for attending this meeting.