



In Vitro Companion Diagnostic Device
Case Studies
2015 AMDM Annual Meeting

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Objectives

Overview

- Companion Diagnostic Case Studies
 - Preapproval Inspection Readiness
 - LDTs as Companion Diagnostics
 - Adequate Sample Selection and Study Design

Overview

IVD companion diagnostic devices

- *In vitro* diagnostic device
- Essential for the safe and effective use of a corresponding therapeutic product
- Labeling in both the diagnostic device and the corresponding therapeutic product

Three FDA Guidance Documents

Published in 2014:

- In Vitro Companion Diagnostic Devices
 - August 06, 2014
- Framework for the Regulatory Oversight of Laboratory Developed Tests
 - October 03, 2014
- FDA Notification and Medical Device Reporting for LDTs
 - October 03, 2014

Case Study #1: Preapproval Inspection Readiness

Overview of 2014 FDA Inspection Findings

- According to the FY 2014 Inspectional Observation Summaries, FDA issued 972 Form 483s
- Of the top 15 cited medical device deficiencies, 10 were for Lack of Procedures
- Other deficiencies noted:
 - Lack of or inadequate process validation
 - Documentation not adequately maintained
 - Lack of Design Control

Preapproval Inspection Readiness

Case Study: BIMO Inspection of Clinical Testing Site

- Therapeutic Area: colorectal cancer
- CDx platform: RT-PCR
- Diagnostic: somatic mutation detection

Preapproval Inspection Readiness

Case Study: BIMO Inspection of Clinical Testing Site

- Diagnostic company contracted with Beaufort to them prepare an EU testing site for a BIMO Inspection
- What Beaufort did:
 - Desktop review of inspection-related documentation
 - Pre-audit clinical testing site
 - Inspection Readiness Training of staff

Preapproval Inspection Readiness

Case Study: BIMO Inspection of Clinical Testing Site

- What Beaufort found:
 - Physical appearance of lab was found in disarray
 - Site unable to easily produce study-related documents
 - Testing site could not accurately characterize the testing they performed
 - Management with executive responsibility was not fully engaged

Preapproval Inspection Readiness

Case Study: BIMO Inspection of Clinical Testing Site

- What Beaufort did to prepare the site for the BIMO:
 - Trained the staff on conduct during the BIMO
 - Brought the MER up to speed
 - Worked with staff on appearance of the lab

Preapproval Inspection Readiness

Case Study: BIMO Inspection of Clinical Testing Site

- Result of BIMO Inspection:
 - No FDA Form 483 was issued
 - Minor verbal comments were issued
- Beaufort recommendation:
 - Maintain the improved QSR moving forward

Preapproval Inspection Readiness

How to Avoid these Common Pitfalls:

- Have SOPs in place for every part of the QSR
 - Management Responsibility
 - CAPA
 - Complaint Handling
 - Design Control
- Robust internal audit program
- Have a third party audit your facility
- Don't forget about clinical testing sites
- Inspection Readiness Training

Case Study #2: LDTs as Companion Diagnostics

Laboratory Developed Tests: an IVD that is intended for clinical use and designed, manufactured and used within a single laboratory

- It has been demonstrated that the development of LDTs as companion diagnostics is supported by Regulatory authorities as an alternative mechanism to traditional IVD kit manufacturing for personalized medicine assays

LDTs as Companion Diagnostics

Case Study: IDE Approval of a Companion Diagnostic LDT

- Therapeutic Area: Cardiovascular disease
- CDx platform: RT-PCR
- Diagnostic: Genotype assay

LDTs as Companion Diagnostics

Case Study: IDE Approval of a Companion Diagnostic LDT

- LabCorp developed a LDT for use in ARCA's GENETIC-AF clinical trial to select patients with the B1389 Arg/Arg genotype, this subset of patients may have a more efficacious treatment response to bucindolol.
 - Test developed and run in one lab

LDTs as Companion Diagnostics

Poster presented at the Heart Failure Society of America 2014 Annual Meeting:

- PERSONALIZED MEDICINE: Prospective Patient Selection Utilizing an ADRB1 Genotype Assay in the GENETIC-AF Clinical Trial. M Bar Hoover, J Albrecht, D Port, and C Dufton, presented at The 18th Annual Scientific Meeting of the HFSA, September 2014



LDTs as Companion Diagnostics

Timeline:

- November 20, 2013: Submit IDE to FDA
- November 26, 2013: Receive email from FDA reviewer requesting the following:
 - Higher concentration of one of the interfering substances
 - An additional interfering substance to be tested
- December 06, 2013: Submit additional information to FDA via email
- December 20, 2013: Receive full IDE approval

LDTs as Companion Diagnostics

FDA Guidance Document:

- Types of Communication During the Review of Medical Device Submissions (April 4, 2014)
 - Interactive Review process is to facilitate the efficient and timely review and evaluation by FDA of premarket submissions through increased informal interaction between FDA and applicants, including the exchange of scientific and regulatory information.

LDTs as Companion Diagnostics

- FDA has approved the IDE for the LabCorp ADBR1 Genotype Assay
- The GENETIC-AF clinical trial is currently ongoing.

LDTs as Companion Diagnostics

Case Study: PMA Approval of a LDT - P140020

- Product Name: BRACAnalysis CDx
- Applicant: Myriad Genetic Laboratories, Inc.
- Approval Date: December 19, 2014

LDTs as Companion Diagnostics

Case Study: PMA Approval of a LDT – P140020

- INDICATIONS FOR USE BRCAAnalysis CDx™ is an *in vitro* diagnostic device intended for the qualitative detection and classification of variants in the protein coding regions and intron/exon boundaries of the BRCA1 and BRCA2 genes using genomic DNA obtained from whole blood specimens collected in EDTA. Single nucleotide variants and small insertions and deletions (indels) are identified by polymerase chain reaction (PCR) and Sanger sequencing. Large deletions and duplications in BRCA1 and BRCA2 are detected using multiplex PCR. Results of the test are used as an aid in identifying ovarian cancer patients with deleterious or suspected deleterious germline BRCA variants eligible for treatment with Lynparza™ (olaparib). This assay is for professional use only and is to be performed only at Myriad Genetic Laboratories, a single laboratory site located at 320 Wakara Way, Salt Lake City, UT 84108.

LDTs as Companion Diagnostics

Case Study: PMA Approval of a LDT – P140020

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Case Study #3: Adequate Sample Selection and Study Design

Case Study: *therascreen*[®] KRAS RGQ PCR kit

- Product Name: *therascreen*[®] KRAS RGQ PCR kit
- Applicant: QIAGEN Manchester Ltd.
- Approval Date: July 6, 2012 (P110030, initial PMA approval)
May 23, 2014 (P110027, 2nd PMA approval)

Adequate Sample Selection and Study Design

Case Study: *therascreen*® KRAS RGQ PCR kit

- Key topics for Approval:

- Adequate analytical characterization of samples/sample preparation
- Method comparison sub-study to demonstrate the accuracy of KRAS mutation detection for use in the clinical trial
- Use of stored samples from a therapeutic trial for a demonstration of safety and effectiveness demonstration for the companion Dx

Adequate Sample Selection and Study Design

Adequate analytical characterization of samples and sample processing

- Testing samples with high necrosis
- Evaluating potential interference from exogenous substances
- Site to site variability - sample processing

Adequate Sample Selection and Study Design

- Method comparison sub-study conducted
- Purpose: to demonstrate the accuracy of KRAS mutation using the Dx kit

Adequate Sample Selection and Study Design

Use of stored samples from a therapeutic trial for a demonstration of safety and effectiveness demonstration for the companion Dx

- High percentage of stored samples were suitable for KRAS kit testing
- Sample inclusion/exclusion criteria were met

Adequate Sample Selection and Study Design

Key Points

- Companion Dx products will continue to emerge in more therapeutic areas and present new “issues” for FDA and the product sponsors
- Talk to FDA early and get closure on key issues affecting speedy approval of a new Companion Dx
- Engage independent experts with past experience in Companion DX to develop a successful regulatory strategy



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