FDA Vision for Novel Technologies

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Agenda

- AbiliLife's Story
- Where to Start and How to Begin
- FDA Strategies and Opportunities
- FDA Labeling
- The Reimbursement Framework
- The Integrated Regulatory & Reimbursement Strategy
- AbiliLife Pre-submission
- Final Conclusions


abiliLife
TM
Story

The Product

Intended Use/Indication for Use:
Back brace designed specifically for Parkinson's patients.

Rolls shoulders up and back for more natural posture.

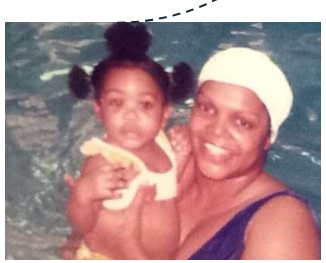
Rigid back panel supports from tailbone to the top of the shoulder blades.

Classification: I, Exempt
Regulation: 21 CFR 890.3490
Description: Truncal Orthosis
Code: IQE

FDA Reg.& Listed # 3011170501

CMS DME-HCPCS Code L047

The Journey



1989

Carnegie Mellon University

2009

BIOMEDICAL ENGINEERING
Carnegie Mellon

2013

alphalab gear

2014

CMS
CENTERS FOR MEDICARE & MEDICAID SERVICES

2015

FDA

2016

NSF

2016

Medical Device Entrepreneurs Address an Unmet Medical Need Through Novel Technology

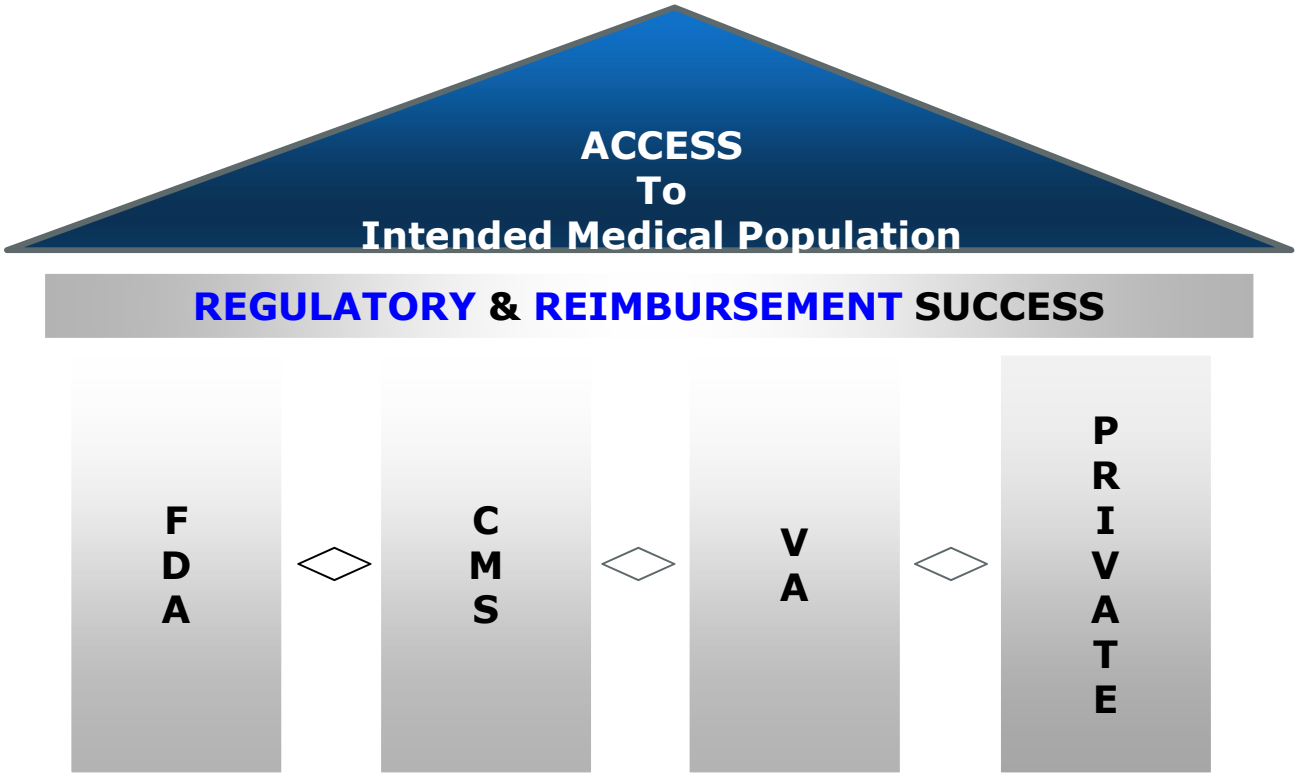
CONCEPTUAL FRAMEWORK

- Personal Experiences
  - Product Vision and Design
- Novel Technology
  - Little/No Precedent
- FDA Purview
  - Potentially rate and cost limiting
- Reimbursement (ROI)
  - Separate from FDA strategy
- Investor Relationship
  - Separate from FDA Strategy

END GOAL: **ACCESS to Intended Medical Population**

Where to Start and How to Begin

YOU THINK THE FDA IS WELL INTENTIONED, BUT WISH IT WOULDN'T HOLD YOU BACK IN YOUR AIM TO SAVE THE WORLD.



ACCESS = PRODUCT SUCCESS =
***Integrated* Regulatory + Reimbursement Strategy**

FDA MISSION: Protect & Promote Health

For Medical Products (Drugs and Devices)

EFFICACY

SAFETY

QUALITY

...POSTMARKETING SURVEILLANCE (safety, supply, manufacture)

FDA Regulates:

$1 trillion worth of products a year

Key FDA Legislation:

Guided by Public Health Events
(> 100 yrs experience)

Legally marketed toxic elixir killed 107 people, including many children

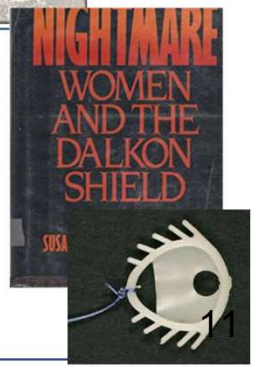
1938: *Federal Food, Drug, and Cosmetic (FD&C) Act* - safety, factory inspections, labeling

EU thalidomide tragedy and FDA's vigilance that prevented the drug's marketing in US

1962: *Kefauver-Harris Amendments* - strengthened safety rules, prove effectiveness

faulty medical devices (including Dalkon Shield) had caused 10,000 injuries, including 731 deaths

1976: The Medical Device Amendments - safety, effectiveness safeguards for devices



FDA Prioritizes:

Innovation

to

Speed Cures and Treatments

➢ **Food and Drug Administration Safety and Innovation Act - FDASIA (2012)**

➢ **21st Century Cures Act (2016)**

- Expedited programs*: *Fast Track, Accelerated Approval, Breakthrough Designation, Priority Review, Humanitarian Device Exemption, Expedited Access Pathway, Regenerative Medicine Advanced Therapy*
- De Novo Pathways for New Medical Device Technology
- Strengthening Clinical Trial Enterprise
- National Evaluation System for Health Technology
- Patient Focused Product Development
- Real-World Evidence
- Balance Pre-Post-Approval Requirements
- Drug and Device Development Tools

➢ **Alliances**

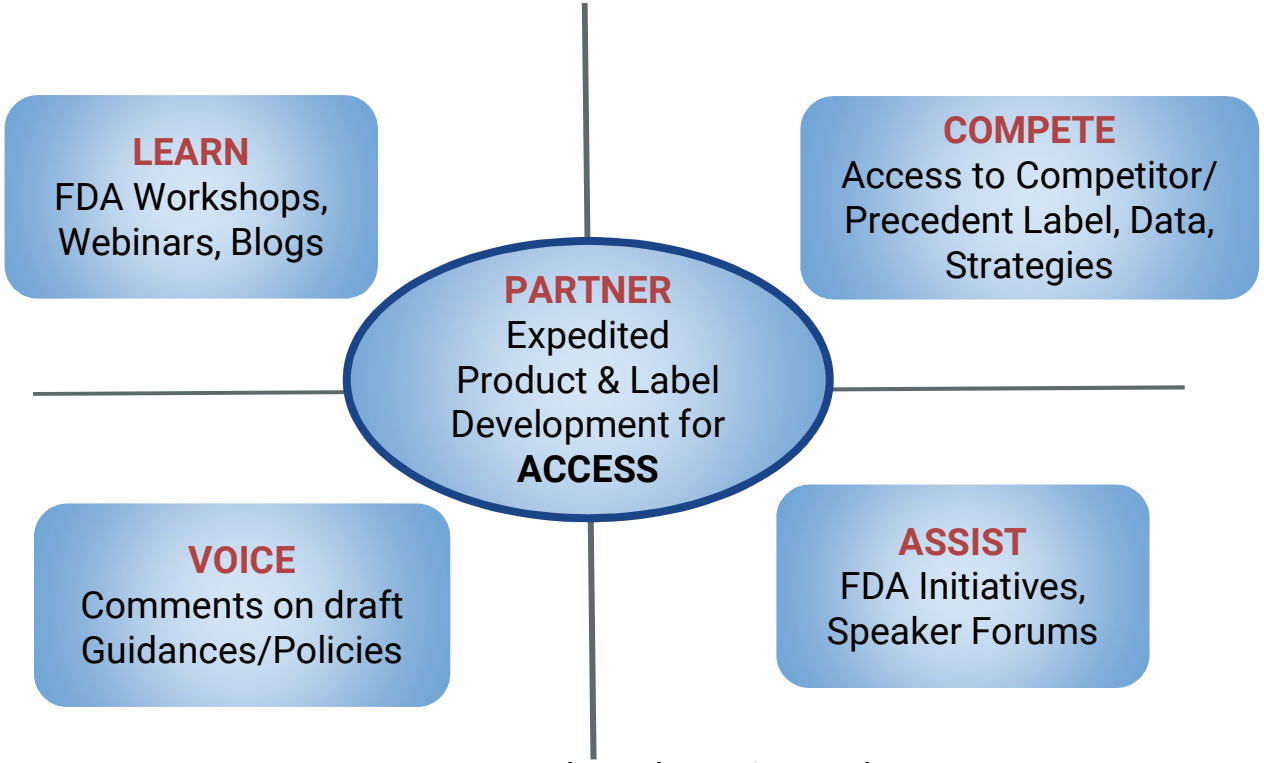
- Academia : CERSI, OSEL *(includes CMU)*
- Global Health Authorities: ICH, IMDRF

* : without lowering standards

2013-2017: Chronic Fatigue Syndrome and Myalgic Encephalomyelitis, Lung Cancer, HIV, Narcolepsy, Idiopathic Pulmonary Fibrosis, Heritable Bleeding Disorders, Inborn Errors of Metabolism, Pulmonary Arterial Hypertension, Fibromyalgia, Sickle Cell Disease, Alpha-1 Antitrypsin Deficiency, Parkinson's Disease and Huntington's Disease, GI Disorders, Chagas Disease, Breast Cancer, Female Sexual Dysfunction, Non-tuberculous Mycobacterial Infections, Psoriasis, Neuropathic pain associated with Peripheral Neuropathy, Organ Transplant, Sarcopenia, Autism, Alopecia Areata, Hereditary Angioedema

FDA Opportunities and Strategies

FDA is an Invaluable Resource



Engage Early and Continuously

Build Lasting Relationship grounded on Collaboration & Integrity

Build Relationship with Patients, Healthcare Community AND Investors

FDA Voice

FDA Enhances Transparency & Learning

Blogs, eNotifications

CDERLearn

CDRHLearn

FDA Meetings, Conferences and Workshops

Basics

- Guidances
- White Papers
- eCFR
- Publications
- Blogs
- Workshops
- Federal Register (Regulations.gov)

Current Information & Opportunity to Comment

Product Specific

- Label
- Review Summaries
- Product Recalls
- Safety Alerts
- Inspection Findings
- Advisory Committee Meetings

Competitive Intelligence for Product Differentiation

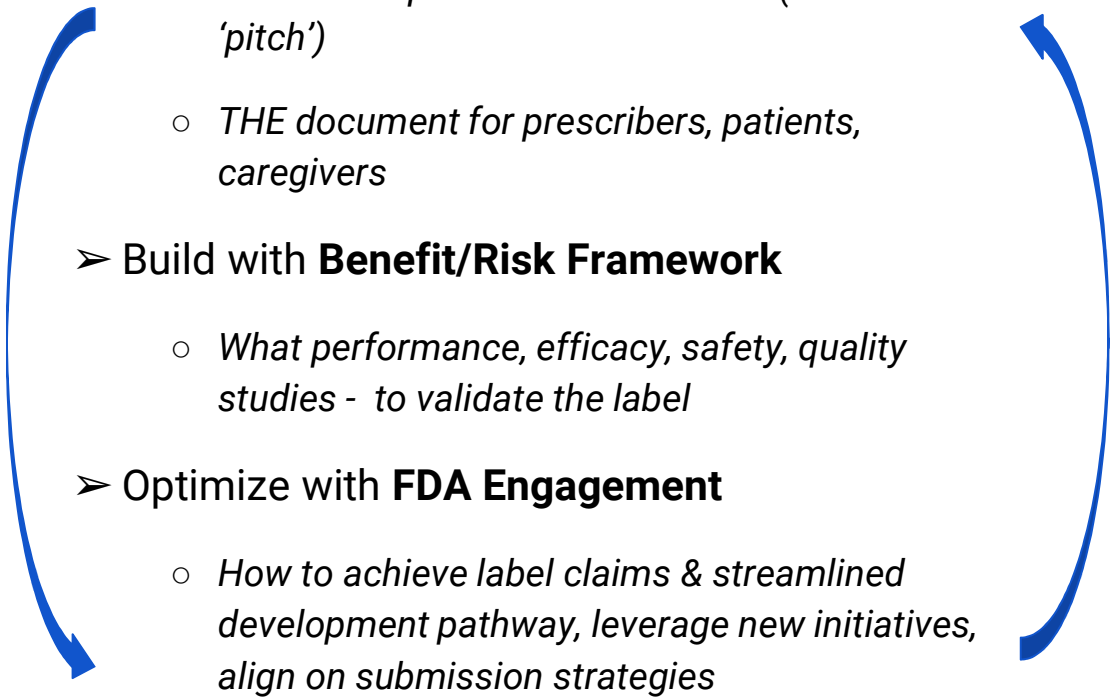
3 Fundamentals for

Expedited Product Development

FDA Submission Strategy

&

Product Differentiation



➢ Start with **Labeling Development**

- *What is the product and its claims (i.e. the 'pitch')*
- *THE document for prescribers, patients, caregivers*

➢ Build with **Benefit/Risk Framework**

- *What performance, efficacy, safety, quality studies - to validate the label*

➢ Optimize with **FDA Engagement**

- *How to achieve label claims & streamlined development pathway, leverage new initiatives, align on submission strategies*

What is Labeling?

What is Labeling

Summary for safe, effective use

For Healthcare Professionals to guide prescription

For Patients, Caregivers for use, decision makimg

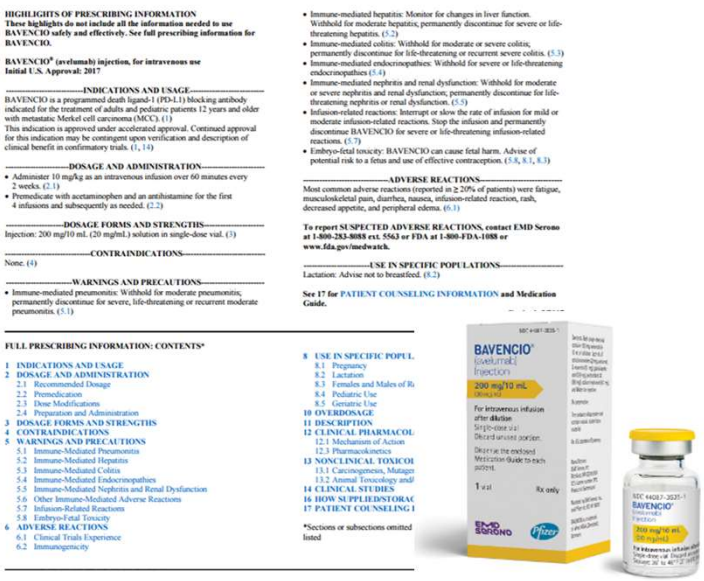
Basis for Advertising, Promotion

Preventing Misbranding

DRUG

Indications

Contraindications, Warnings, Precautions
Dosage
Mechanism of Action
Clinical Pharmacology
Safety
Efficacy
Supply



HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BAVENCIO safely and effectively. See full prescribing information for BAVENCIO.

BAVENCIO® (avelumab) injection, for intravenous use
Initial U.S. Approval: 2017

INDICATIONS AND USAGE

BAVENCIO is a programmed death ligand-1 (PD-L1) blocking antibody indicated for the treatment of adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma (MCC). (1)
This indication is approved under accelerated approval. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1, 14)

DOSAGE AND ADMINISTRATION

- Administer 10 mg/kg as an intravenous infusion over 60 minutes every 2 weeks. (2.1)
- Premedicate with acetaminophen and an antihistamine for the first 4 infusions and subsequently as needed. (2.2)

DOSAGE FORMS AND STRENGTHS

Injection: 200 mg/10 mL (20 mg/mL) solution in single-dose vial. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Immune-mediated pneumonitis: Withhold for moderate pneumonitis; permanently discontinue for severe, life-threatening or recurrent moderate pneumonitis. (5.1)
- Immune-mediated hepatitis: Monitor for changes in liver function. Withhold for moderate hepatitis; permanently discontinue for severe or life-threatening hepatitis. (5.2)
- Immune-mediated colitis: Withhold for moderate or severe colitis; permanently discontinue for life-threatening or recurrent severe colitis. (5.3)
- Immune-mediated endocrinopathies: Withhold for severe or life-threatening endocrinopathies (5.4)
- Immune-mediated nephritis and renal dysfunction: Withhold for moderate or severe nephritis and renal dysfunction; permanently discontinue for life-threatening nephritis or renal dysfunction. (5.5)
- Infusion-related reactions: Interrupt or slow the rate of infusion for mild or moderate infusion-related reactions. Stop the infusion and permanently discontinue BAVENCIO for severe or life-threatening infusion-related reactions. (5.7)
- Embryo-fetal toxicity: BAVENCIO can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception. (5.8, 8.1, 8.3)

ADVERSE REACTIONS

Most common adverse reactions (reported in ≥ 20% of patients) were fatigue, musculoskeletal pain, diarrhea, nausea, infusion-related reaction, rash, decreased appetite, and peripheral edema. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact EMD Serono at 1-800-283-8088 ext. 5563 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

FULL PRESCRIBING INFORMATION: CONTENTS*

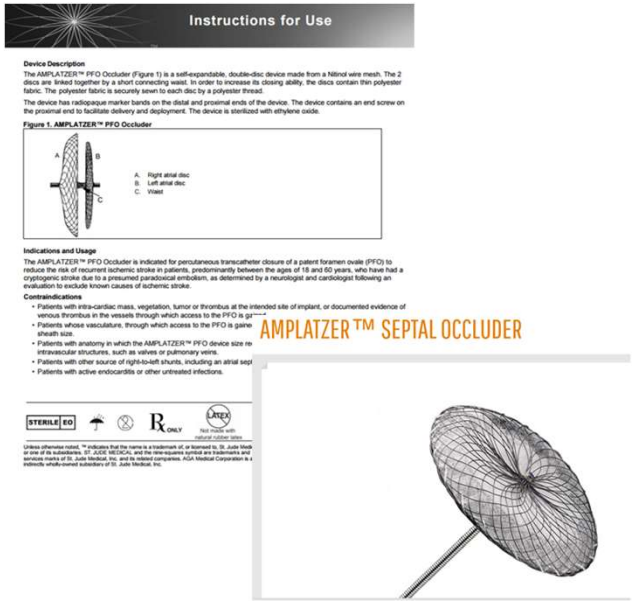
*Sections or subsections omitted listed

DEVICE

Intended Use

Indications for Use

Contraindications, Warnings, Precautions
Instructions for Use: Physician, Patient
Device Description
Specifications
Safety
Effectiveness



Instructions for Use

Device Description

The AMPLATZER™ PFO Occluder (Figure 1) is a self-expandable, double-disc device made from a Nitinol wire mesh. The 2 discs are linked together by a short connecting waist. In order to increase its closing ability, the discs contain thin polyester fabric. The polyester fabric is securely sewn to each disc by a polyester thread.

The device has radiopaque marker bands on the distal and proximal ends of the device. The device contains an end screw on the proximal end to facilitate delivery and deployment. The device is sterilized with ethylene oxide.

Figure 1. AMPLATZER™ PFO Occluder

A. Right atrial disc
B. Left atrial disc
C. Waist

Indications and Usage

The AMPLATZER™ PFO Occluder is indicated for percutaneous transcatheter closure of a patent foramen ovale (PFO) to reduce the risk of recurrent ischemic stroke in patients, predominantly between the ages of 18 and 60 years, who have had a cryptogenic stroke due to a presumed paradoxical embolism, as determined by a neurologist and cardiologist following an evaluation to exclude known causes of ischemic stroke.

Contraindications

- Patients with intra-cardiac mass, vegetation, tumor or thrombus at the intended site of implant, or documented evidence of venous thrombus in the vessels through which access to the PFO is ga
- Patients whose vasculature, through which access to the PFO is gaine sheath size.
- Patients with anatomy in which the AMPLATZER™ PFO device size re intravascular structures, such as valves or pulmonary veins.
- Patients with other source of right-to-left shunts, including an atrial sep
- Patients with active endocarditis or other untreated infections.

AMPLATZER™ SEPTAL OCCLUDER

STERILE EO

Rx ONLY

Latex

What is a Drug or a Device?

Per the FD&C Act

DRUG or DEVICE defined by its INTENDED USE

Intended for use in DISEASE

- Diagnosis
- Cure
- Mitigation
- Treatment

Intended to AFFECT STRUCTURE or any FUNCTION of the body

Does not achieve any of its primary intended purposes through **CHEMICAL ACTION** within or on the body (Device only)

LABELING

Case Study: Mar 2017

The NY General's office settled with three mobile health apps alleged misleading claims and irresponsible privacy practices

- **Adidas subsidiary Runtastic**
- **MIT Media Lab spinoff Cardiio**
- **Matis, maker of "My Baby's Beat"**

Did not function as advertised

Made misleading claims

Did not protect sensitive user information

Labeling Strategy & Product Differentiation drive Submission Strategy

LABELING

MVP	OPTIMIZE	EXPAND
Min. Claim Low/Mod Risk	Add Claims ⩾ Risk	New Tech, New Use ⩾ Risk

Identify Least Burdensome Pathway to Achieve Desired Labeling

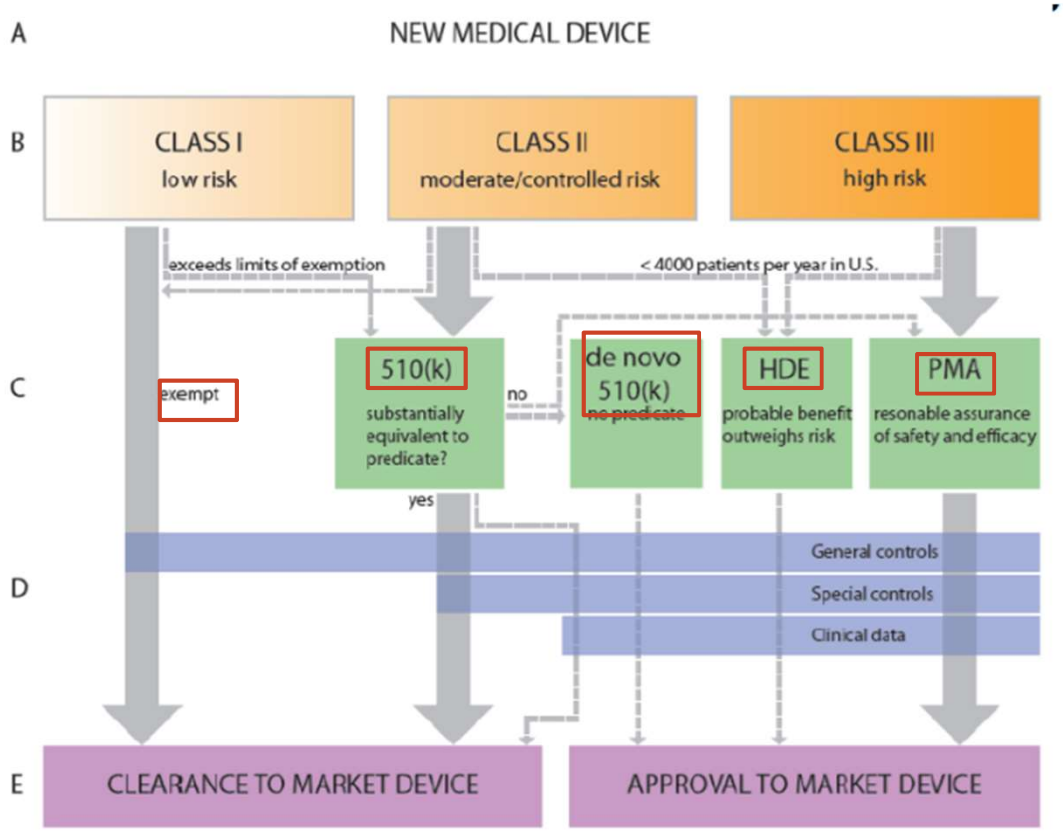
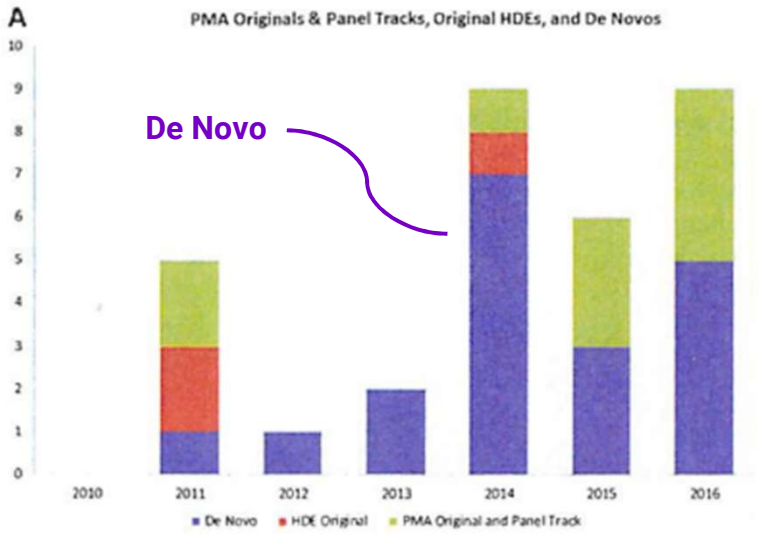


Figure Source: FDA

De Novo Pathway for Startups

Increasing Trend for New Technology



Devices that aren't comparable enough to a marketed device

Generates New Classification Regulation, Class I/II

★ FDA eager to engage on New Technology

★ No Submission Fee

★ Reasonable Review timelines (120 d)

★ Directly contribute to New Classification Regulation (*guided by Proposed Labeling!)*

★ First to Market

What is FDA Engagement (no fees)

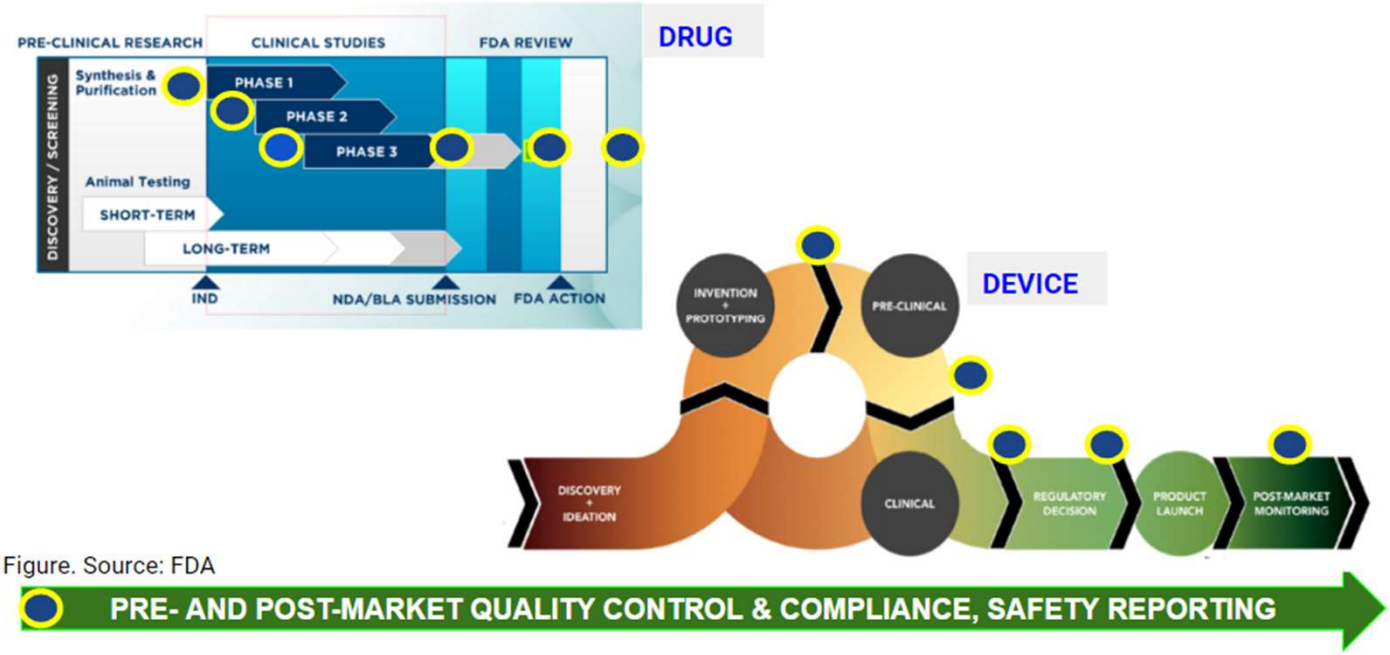


Figure. Source: FDA

Formal Meetings

DRUGS

Type A, B, C Meetings
Pre-IND
End-of-Phase 1
End-of-Phase 2 (EOP2)
Pre-NDA
During and Post-NDA

DEVICES

Pre-Submission
Informational
Study Risk Determination
Agreement Meeting
Determination Meeting
Submission Issue meeting
Day 100 Meeting

Also available via Phone, Email

Case Study: Mar 20, 2017

Array BioPharma Provides NEMO Update

- NRAS-mutant melanoma NDA withdrawn based on thorough discussions with FDA and following late cycle review meeting -

Array walks back its FDA pitch on binimetinib, derailing plans for commercial launch

Fifteen months after the Boulder, CO-based **biotech said that it had the data needed for its first approval** of binimetinib for NRAS-positive melanoma, execs are walking back the application and its plans for a launch.

In a statement out Sunday evening, Array $ARRY said that **after getting feedback from the FDA**, execs "concluded that the clinical benefit demonstrated in the Phase 3 NEMO **clinical trial would *not* be found sufficient** to support approval of the NRAS-mutant melanoma NDA."

Shares of Array dropped 26% in pre-market trading Monday.

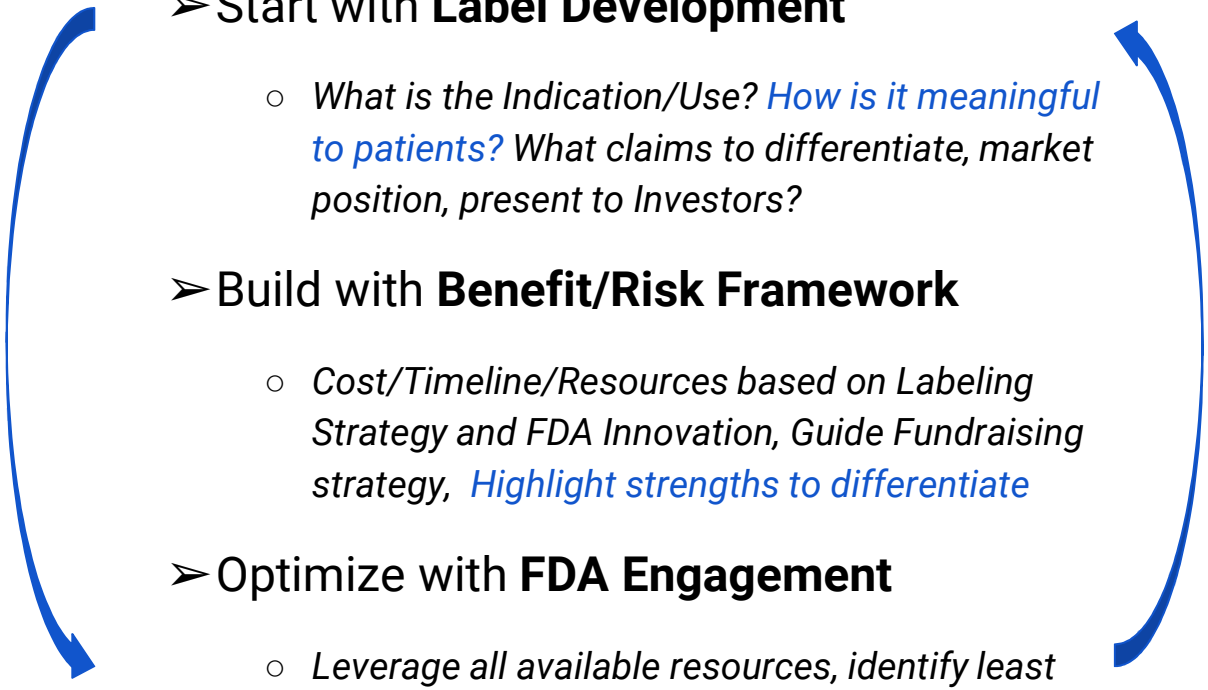
Losing Nemo: Array pulls skin cancer NDA for binimetinib

value driver for the company: "We think this comes as a surprise to investors and is a clear setback for the company and management's regulatory and commercial strategy."

Engaging with FDA as a Startup

To

Ensure ACCESS to Intended Population



➢ Start with **Label Development**

- *What is the Indication/Use? How is it meaningful to patients? What claims to differentiate, market position, present to Investors?*

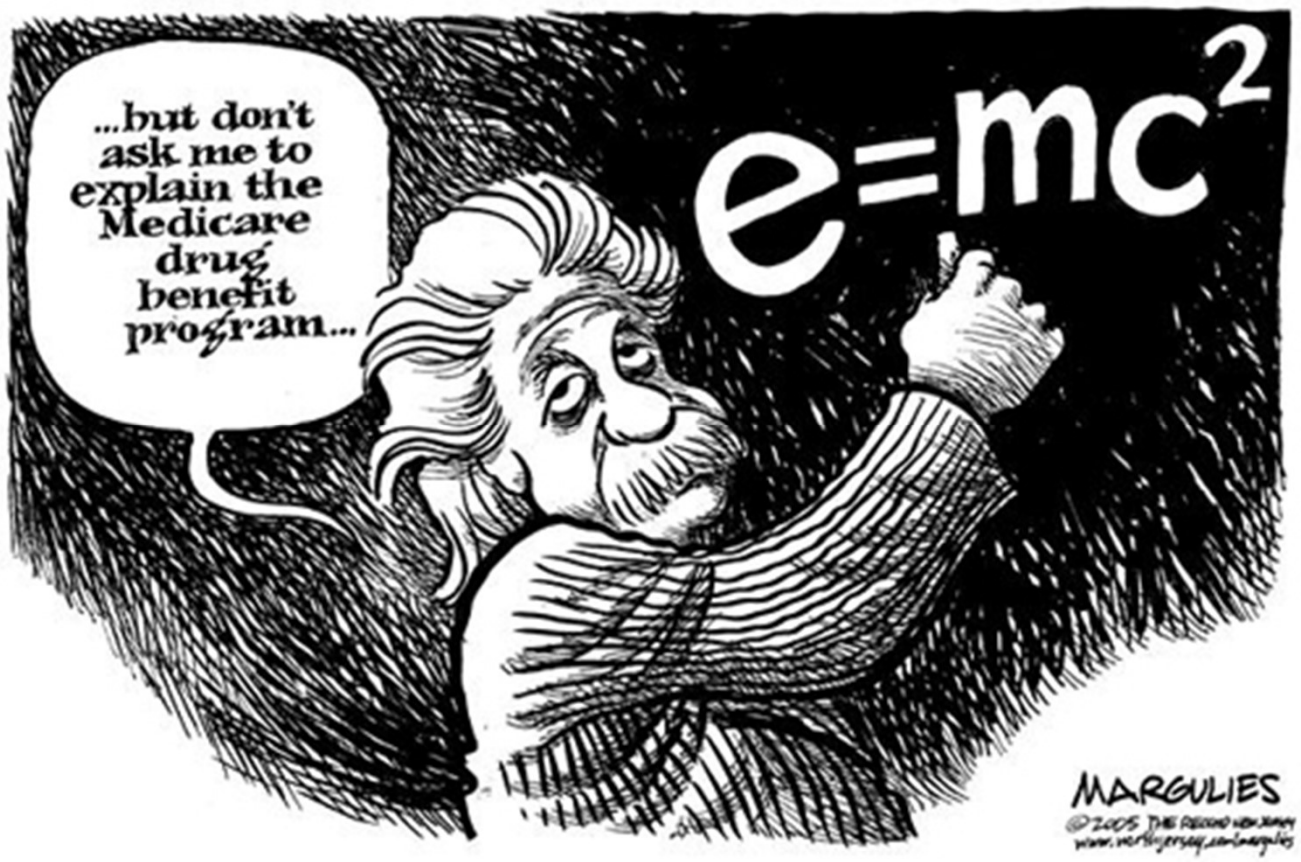
➢ Build with **Benefit/Risk Framework**

- *Cost/Timeline/Resources based on Labeling Strategy and FDA Innovation, Guide Fundraising strategy, Highlight strengths to differentiate*

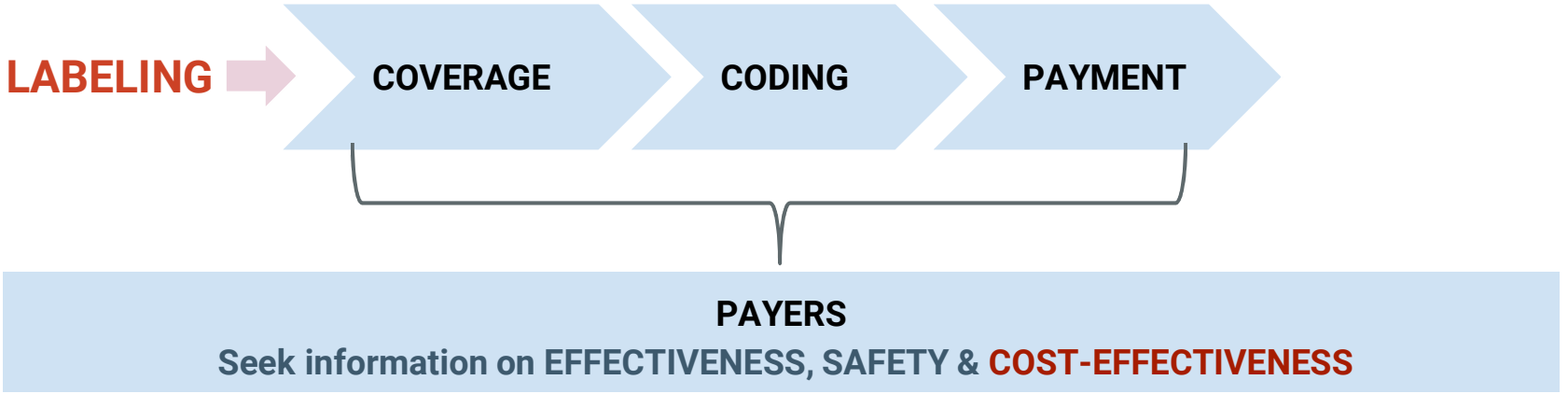
➢ Optimize with **FDA Engagement**

- *Leverage all available resources, identify least burdensome strategy(s), Explore novel approaches to enhance value, Gain visibility by engaging in initiatives*

The Reimbursement Framework


...but don't ask me to explain the Medicare drug benefit program...
e=mc²
MARGULIES

Reimbursement: Essential for ACCESS



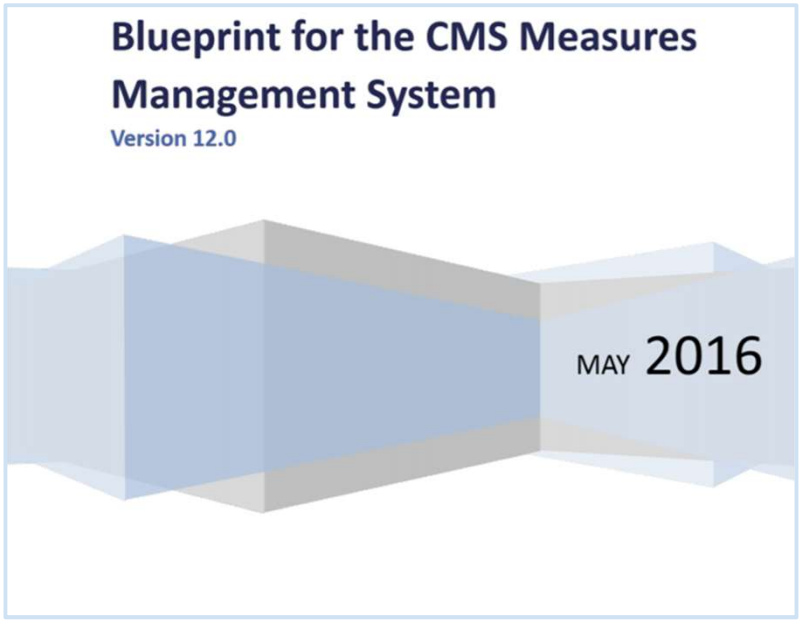
CMS.gov

- Centers for Medicare & Medicaid Services, DHHS
- Formed by the Social Security Act
- Seeks Health Care Economic Information

Department of Veterans Affairs · BlueCross BlueShield · Humana · KAISER PERMANENTE

Similar Criteria; Interagency Agreements, Contracts

CMS' Evolving Strategies share commonalities with FDA's Guidances, Innovation Initiatives



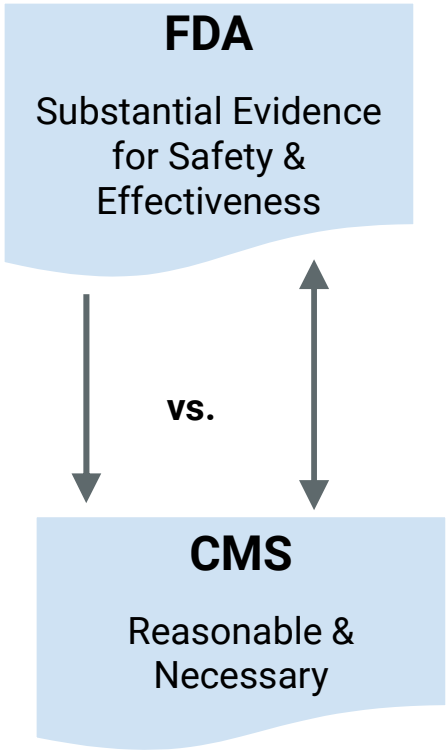
Transitioning from a Fee for Service (FFS) system to a **payment system based on quality and value**

6 Goals to improve the quality of care

1. Make Care Safer
2. Strengthen Person and Family Engagement
3. Promote Effective Communication and Coordination of Care
4. Promote Effective Prevention and Treatment
5. Work with Communities to Promote Best Practices of Healthy Living
6. Make Care Affordable

The Integrated Regulatory & Reimbursement Strategy

FDA vs CMS: Integrate and Engage Early



GENERAL Approach - Fragmented

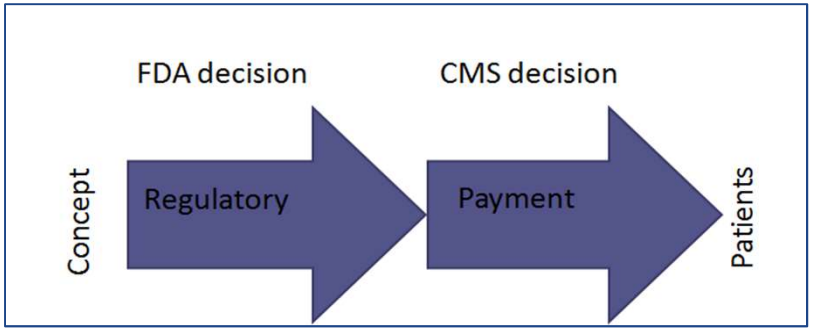
1. FDA approval/clearance
2. Approval for coverage and payment
3. *May need additional studies to address Payer requirements*

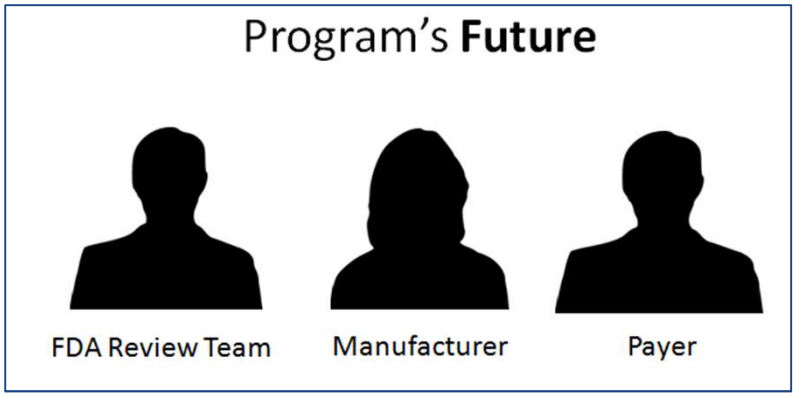
INTEGRATED Approach - Simultaneous

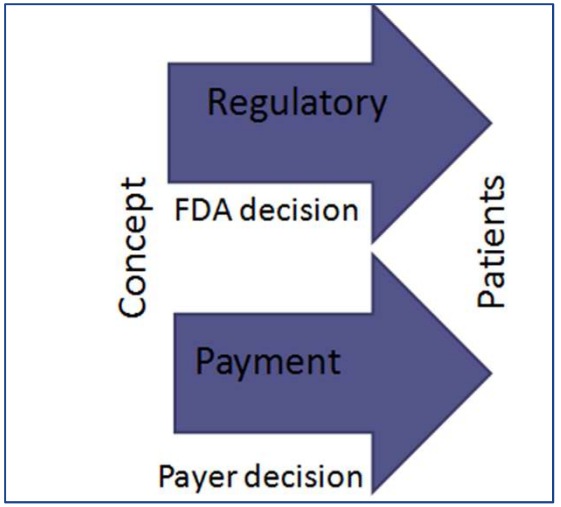
Leverage shared evidence source for both Agencies while addressing criteria for decision making

CMS and FDA's Regulatory Review & Coverage Coordination

Rochelle Fink, M.D., J.D.–
FDA-CMS Liaison
Center for Devices & Radiological Health
U.S. Food and Drug Administration







CDRH Innovation:

Payer Communication Task Force (PCTF)

- Opportunities to **Obtain Payer Input Simultaneously with FDA**
  a. Pre-Submission Participation
  b. Parallel Review Program
- Potentially **shorten time** between FDA approval/ clearance and actual coverage decisions
- By **communicating earlier**, **design clinical trials** for regulatory approval/clearance and positive coverage determination
- **Participating Payers:** CMS, BlueCross BlueShield, Humana, Kaiser Permanente, NICE (UK!)

→ Discuss and Align on Clinical program with FDA + Payer at Pre-Submission Meeting

→ FDA PCTF co-ordinates participation of CMS + Other payers

Parallel Review Program: The Stats

2011: Pilot Program initiated

2013: Pilot Program extended

2016: Program fully implemented

> 60 inquiries, 29 applications

Several Pre-Submission Meetings have likely occurred

2014

cologuard Rx only

FDA News Release

FDA approves first non-invasive DNA screening test for colorectal cancer

Collaboration with CMS contributed to proposed Medicare coverage

2016

FOUNDATION MEDICINE

Aug 2, 2016

FoundationOne® Accepted by FDA and CMS for Parallel Review and FDA Expedited Access Pathway

Engaging with FDA & Payer as a Startup

for

Expedited ACCESS to Intended Population

➢ Start with **Label Development**

- *Address FDA and Payer needs - focus on the **value** to patients, caregivers, medical community*

➢ Build with **Benefit/Risk & Cost-Effectiveness Framework**

- *Address FDA and Payer needs in pivotal study*

➢ Optimize with **FDA & Payer Engagement**

- *Obtain FDA clearance/approval and Local/national coverage in a timely manner*

AbiliLife Pre-Submission

Label Development : Differences in wording impacting Evidentiary Requirements and Submission Strategy

Alert for High Fall Risk

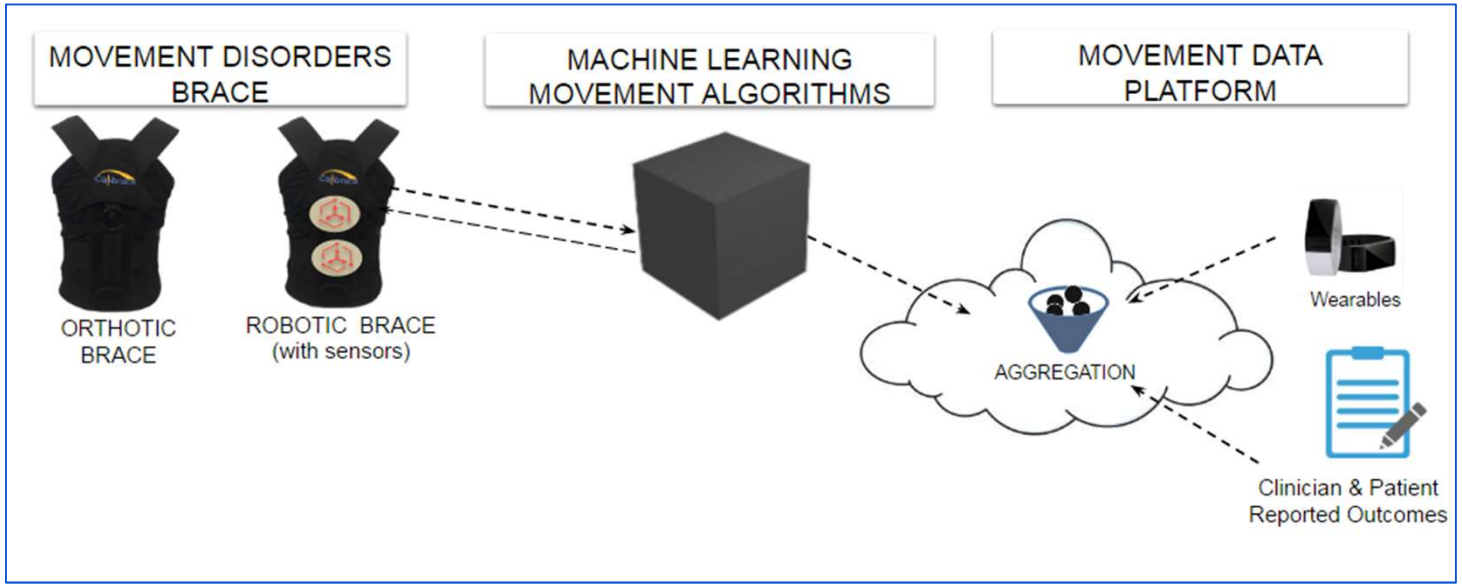
Versus

Prevention of Fall

*business decision

Pre-Sub Meeting led to Portfolio Enhancement Opportunities

BEFORE Pre-Submission

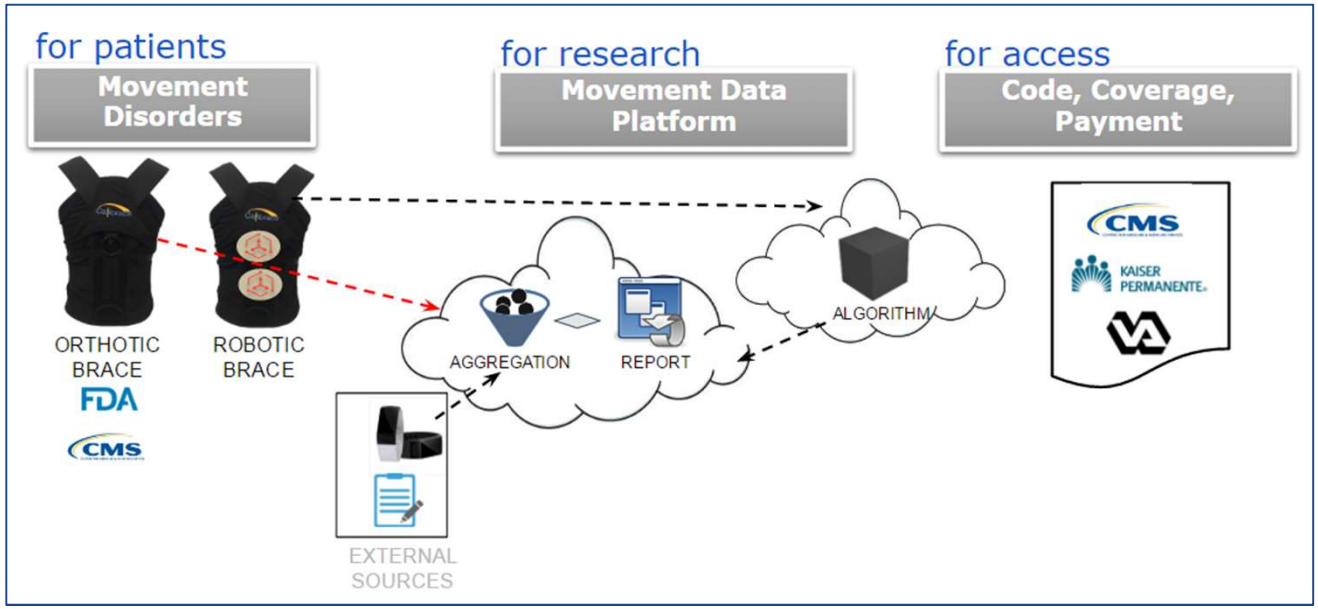


- 1 Medical Device pathway - Fee for Subm.
- FDA purview (?) of Non-Device Platform
- FDA assistance (?) for CMS engagement
- Interaction with CDRH Review Branch

Pre-Sub Meeting led to Portfolio Enhancement Opportunities

AFTER Pre-Submission

- 1 Medical Device pathway - No fee
- 3 FDA Designations for Platform - No Fee
- Streamlined Strategies for Studies
- Facilitated Engagement with CMS
- Facilitated Engagement with Private Payer
- Expanded scope of FDA Interactions



Software Development Prototype

```
import botocore
import boto3
import matplotlib.pyplot as plt
import numpy as np

s3_resource = boto3.resource('s3')
s3 = boto3.client('s3')
ans = np.array([])
output = np.array([])
interval = 2


try:

    bucket = 'example32317'
    response1 = s3.list_objects(
        Bucket=bucket)
    for obj in response1["Contents"]:
        key = obj["Key"]
```

AWS Lambda

Dashboard

Functions

Code | Configuration | Triggers | Monitoring

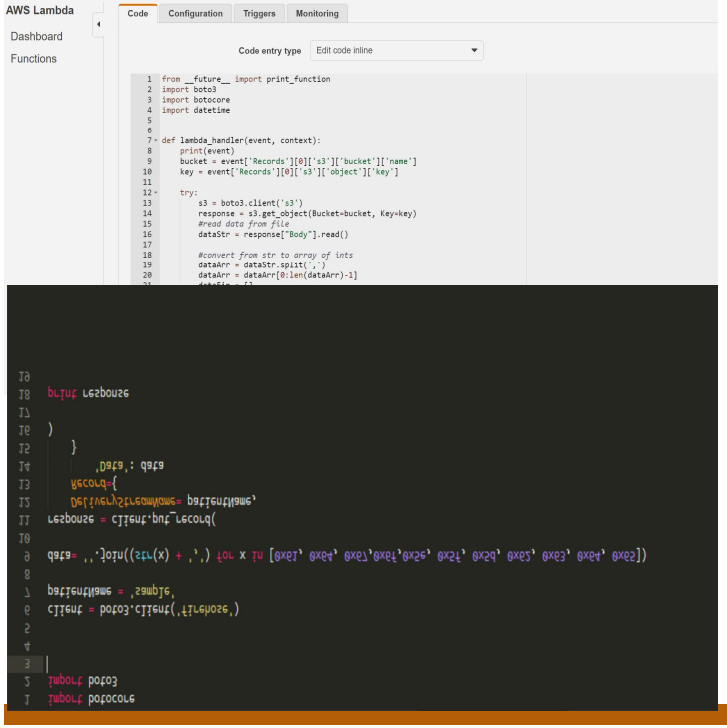
Code entry type: Edit code inline

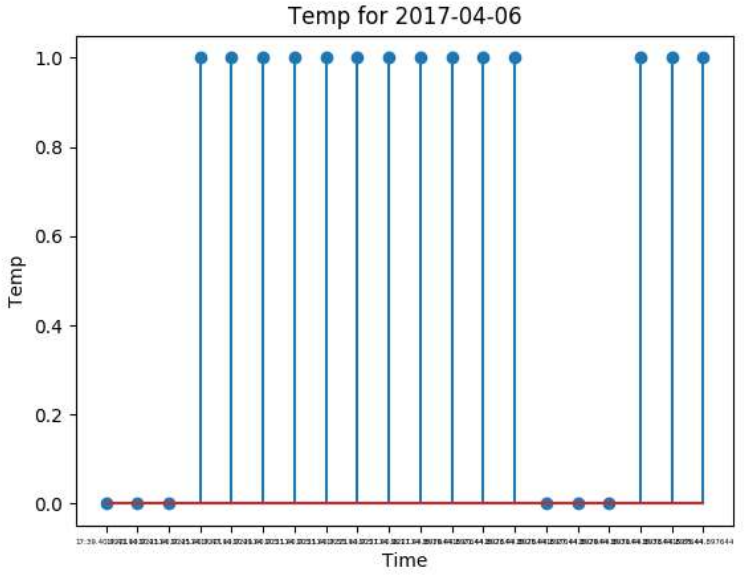
```
from __future__ import print_function
import boto3
import botocore
import datetime


def lambda_handler(event, context):
    print(event)
    bucket = event['Records'][0]['s3']['bucket']['name']
    key = event['Records'][0]['s3']['object']['key']

    try:
        s3 = boto3.client('s3')
        response = s3.get_object(Bucket=bucket, Key=key)
        #read data from file
        dataStr = response["Body"].read()

        #convert from str to array of ints
        dataArr = dataStr.split(',')
        dataArr = dataArr[0:len(dataArr)-1]
```





Continuum of CDRH Engagement

to Optimize

Regulatory & Reimbursement Strategy

Alignment of Label/Development/Submission Strategies

- F2F Pre-Submission Meeting
  - Several email/ phone calls with Document Control Center, Branch Chief and Lead Reviewer prior to meeting

Additional Product Registration Strategies

- Phone/Email with Master File (MAF) Office
- Phone/Email with Medical Device Development Tool (MDDT) Program Office
- Phone/Email with OSEL

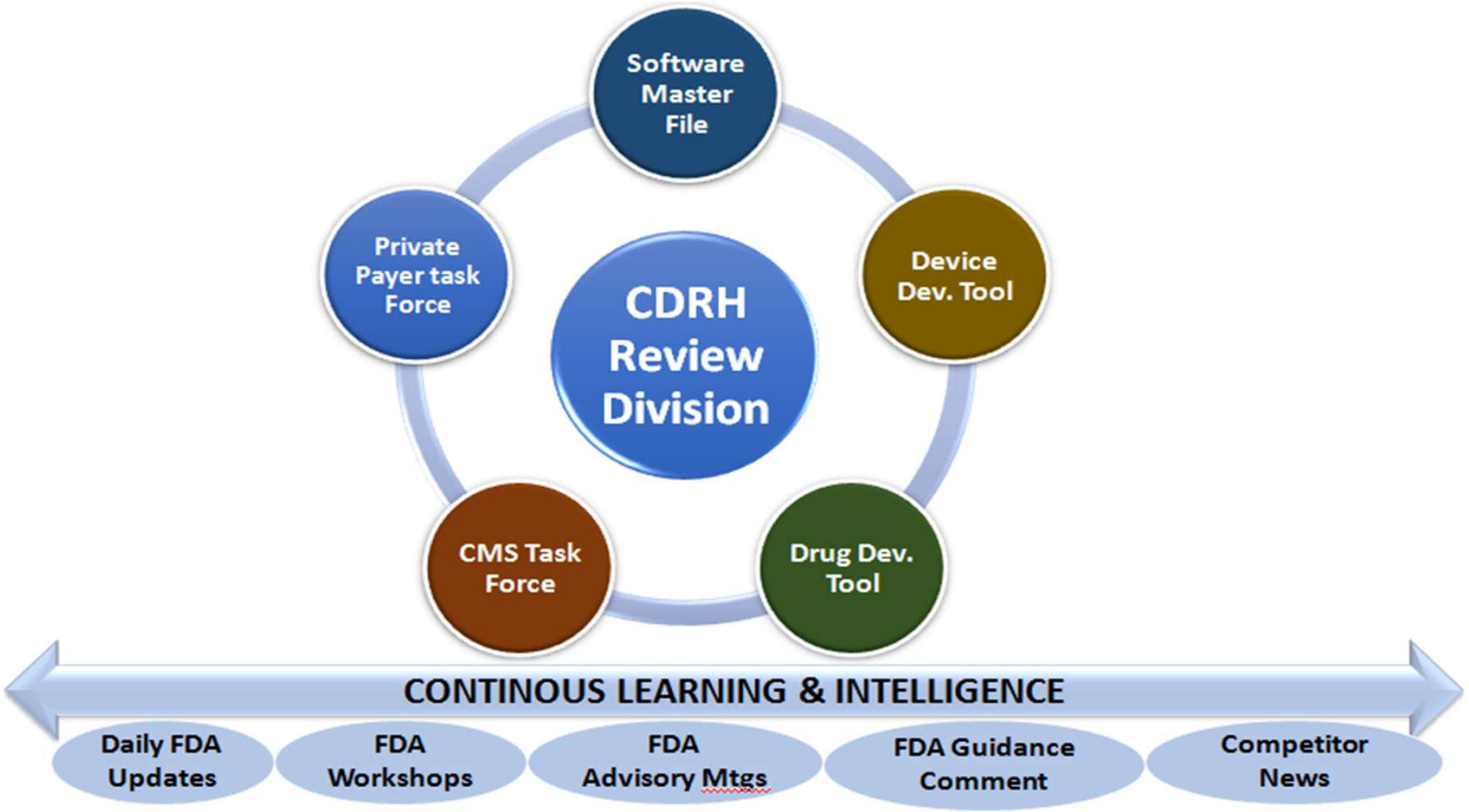
CMS Engagement

- Phone/Email with CMS Point of Contact
- Phone/Email with PCTF office

Followup on Optimized AbiliLife Portfolio

- T/C with Lead Reviewer

FDA Engagement & Learning: Continuous, Multi-Faceted



Final Conclusions

Impact of FDA Engagement on

External Communications

Portfolio Value Enhancement

Integrated processes between FDA strategy and business development

E.g. Manufacturer, Distributor, Investor, Grant Applications

Value Assessment of Portfolio

Summary of Learnings as an Entrepreneur

- Interact with the FDA early and often
- Make sure that your investors understand the FDA process
- View the FDA as a partner and not as a foe
- Understand the value of having an FDA approved product for when you value your company