CONNECTS Seminar

FDA Vision for Novel Technologies

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Swartz Center for Entrepreneurship

April 3, 2018

Agenda

AbiliLife's Story

Understanding the FDA

Beyond First FDA Marketing Authorization

AbiliLife FDA Engagement and Product Roadmap

Conclusions

Story

The Product

Intended Use/Indication for Use:
Back brace designed specifically for neuromuscular patients (i.e. Parkinson's disease, ALS, MS).

Rolls shoulders up and back for more natural and healthy 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

CMS CENTERS FOR MEDICARE & MEDICAID SERVICES

Reg.& Listed # 3011170501
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

Post-Marketing : 2016 - Today

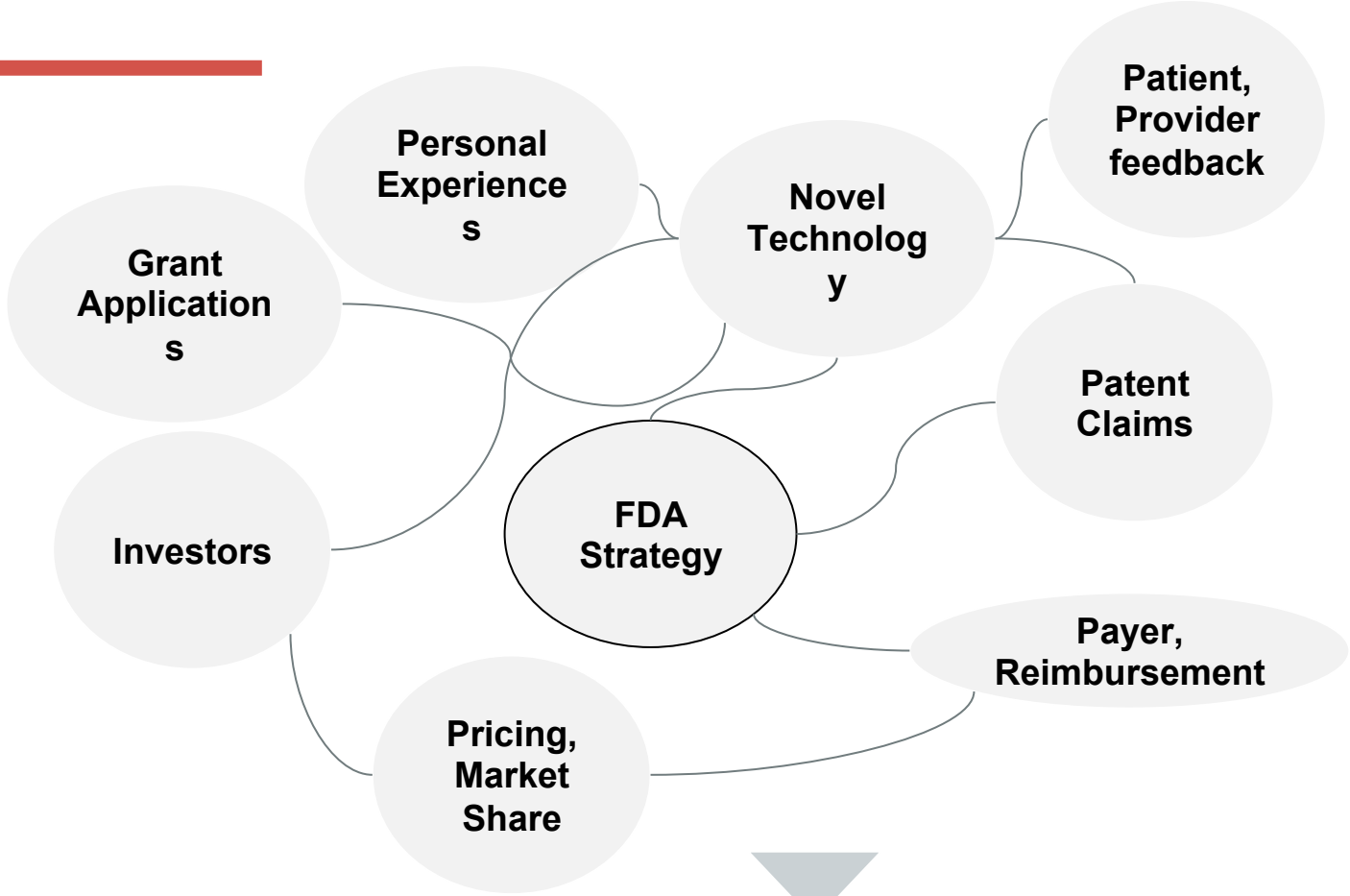
Originally designed for PD patients

Sole-providership helped with payment

600 Pre-existing codes didn't include PD

Plans to submit for a PD specific claim

The Web:
FDA Strategy Interlinked with Innovation And Business Needs



Meet Patient, Caregiver, Business Needs
Advance Science

Understanding the FDA

https://
www.fda.gov

FDA Regulates: $1 trillion worth of products a year

FDA Mission: Protect & Promote Health

FDA Modernization: Streamline, Expedite, Incentivize, Least Burdensome Approach*

* : Minimum amount of necessary information, most efficient manner, right time

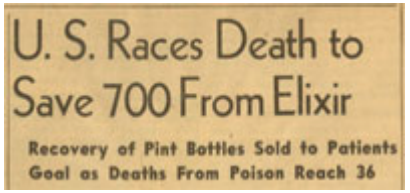
EXAMPLES

FDA Legislation:

Guided by Public Health Events

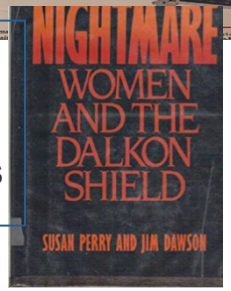
> 100 yrs experience

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, thousands of babies with malformed limbs - 1962: ***Kefauver-Harris Amendments*** safety rules, prove effectiveness

Faulty medical devices (Dalkon Shield) - caused 10,000 injuries, 731 deaths 1976: **The Medical Device Amendments** safety, effectiveness safeguards for devices



2017-2018 Flu Season- many deaths including > 100 children; vaccine not fully effective. 2018: **FDA plan of Action** including updating vaccine requirements

Is it a Drug or a Device?

Per the FD&C Act

Intended for use in DISEASE

- **D**iagnosis (disease, conditions)
- **C**ure
- **M**itigation
- **T**reatment
- **P**revention

AFFECT STRUCTURE or any FUNCTION of body

CHEMICAL ACTION within or on body (Drug only)

Medical Products & FDA Submission Pathways

DRUGS: Small Molecule, Biologics

NDA, BLA..and Supplements

ANDA, 505B(2)

DEVICES: Hardware, Hardware+Software, Software only

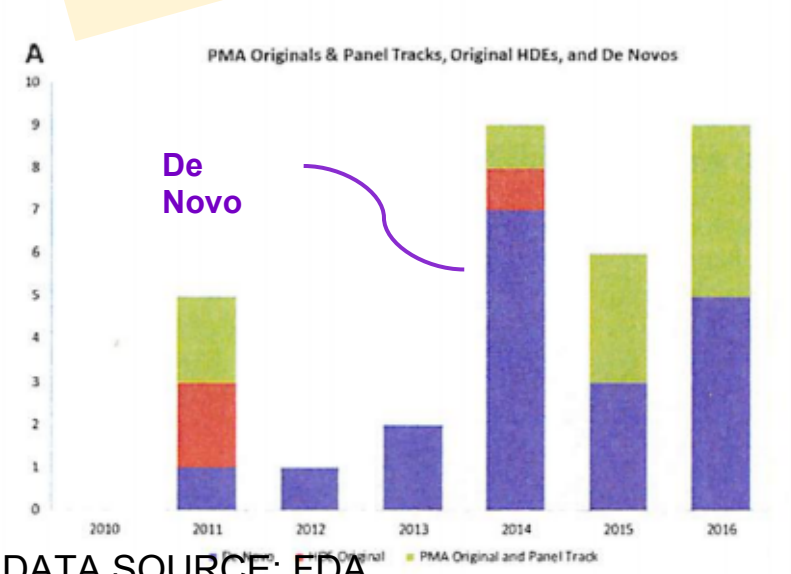
Exempt, 510(k), De Novo, PMA, HDE

COMBINATION PRODUCT

Jurisdiction, Request for Designation

Highlight: De Novo Pathway

Trending for CMU Startups



DATA SOURCE: FDA

NOVEL TECHNOLOGY, not comparable to a marketed product

Promote New Technology

Reasonable Review timelines (150 d)

Create New Classification Regulation

Trailblazing..unique device showcasing new technology

First to Market

Delay competition

FDA Drug/ Device Development Overview

Drug and Device Development

LINK

READ

1 **DISCOVERY/ CONCEPT**	Research for a new drug or device begins in the laboratory...maker space….garage
2 **PRECLINICAL**	Laboratory and animal testing to answer basic questions about safety, prototyping
3 **CLINICAL**	Human testing for safety and effectiveness
4 **FDA REVIEW**	*Thorough* examination of all submitted data; approval or non approval
5 **POST-MARKET MONITORING**	Monitoring safety once products available for use by public

Key Review Elements

Based on:

Valid **Scientific Evidence**

&

Totality of **Evidence**

Product Label

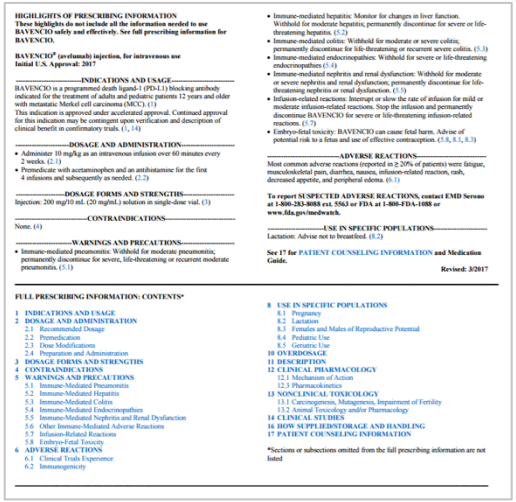
Primary source for differentiation, patient access, commercial success

Basis of FDA review, approval

Guide:
Effective use
Prescription
Patient decision

Source:
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)

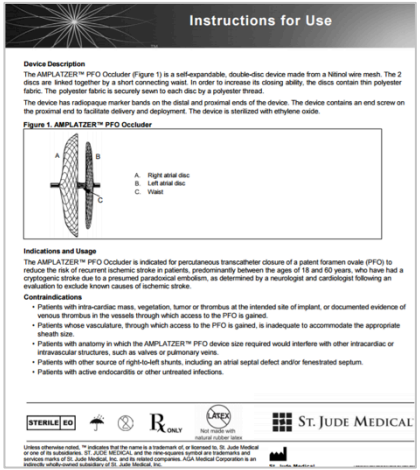
See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 3/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not 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

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 gained.
- Patients whose vasculature, through which access to the PFO is gained, is inadequate to accommodate the appropriate sheath size.
- Patients with anatomy in which the AMPLATZER™ PFO device size required would interfere with other intracardiac or intravascular structures, such as valves or pulmonary veins.
- Patients with other source of right-to-left shunts, including an atrial septal defect and/or fenestrated septum.
- Patients with active endocarditis or other untreated infections.

STERILE EO ℞ ONLY Not made with natural rubber latex ST. JUDE MEDICAL

FDA Prioritizes:

INNOVATION

'...to Speed Cures and Treatments without Lowering Standards..'

Streamlining and Modernizing

De Novo Pathways for New Medical Device Technology, Personalized medicine, Strengthening Clinical Trial Enterprise, National Evaluation System for Health Technology, Patient Focused Development, Real-World Evidence, Adaptive Design, Modeling/Simulation, Balance Pre and Post-Approval Requirements, Drug and Device Development Tools…..

New Technology

3D Printing, Model informed development, Software as Medical Device, Clinical Decision Support, Patient Decision Support……...

Small Business Incentives

User Fee Reductions , Grants (SBIR), SBIA, DICE, Small Business Investments, Licensing and Collaboration…….

Other Incentives

Rare Disease programs, Expedited/Priority Reviews, Fast Track, Breakthrough, Priority Review Vouchers……..

Alliances

CMS and Private Payors, Academia *(includes CMU),* Small Business, Global Health Authorities……..

FDA Prioritizes: INNOVATION

Digital Health / AI

2017: Software Precertification Program

Digital health technology with focus on software developer or digital health technology developer

- Apple
- Fitbit
- Johnson & Johnson
- Pear Therapeutics
- Phosphorus
- Roche
- Samsung
- Tidepool
- Verily

2018: AI/Machine Learning Guidances

- Clinical Decision Support Software
- Patient Decision Support Software

STARTUP IS TOUGH

Novel Products

Competition

Budget

Resources

Funding

Investors

Timelines

ROI

Evolving Landscape

Information Overload

Unclear Pathway

REG STRATEGY HELPS

START EARLY

Grounded in Science, Data, Evidence, Quality

Novel Product Development Approaches

Adapt to pivots, unexpected data, resource constraints

Optimize design to support desired label

ENGAGE WITH FDA

Opportunities, Incentives Expedite

Competitive Differentiation Business Strategies

GET DESIRED LABEL

3 FUNDAMENTALS

Of Regulatory Strategy

'...begin with the end in mind..'

1 **Labeling Development**

What is the Indication and desired claims ***(pitch, patent, differentiation, reg intell.)***

2 **Benefit/Risk Framework**

What performance, efficacy, safety, studies - to substantiate label ***(roadmap, funding, investor plans, timelines)***

What Quality measures to ensure continued safety and efficacy ***(culture of excellence)***

3 **FDA Engagement** ***(long-term partnership)***

How to achieve label claims

Opportunities, Incentives to streamline

Leverage new initiatives

Lower cost and time

Align on submission strategies

FDA Engagement

Formal FDA Meetings:
e.g. Pre-Submission, Pre-IND, EOP2, Pre-NDA.

Regulatory Intelligence

Continual evolution of landscape

Continual learning is a must

FDA Tutorials
- CDER Learn

Basics

Code of Federal Regulations
Guidances
White Papers
Publications
Blogs
Priorities
Workshops
Federal Register (Regulations.gov)

Current and Emerging Regs

Expedite, Streamline

Incentives

Comment

Product Specific

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

Precedents

Competition

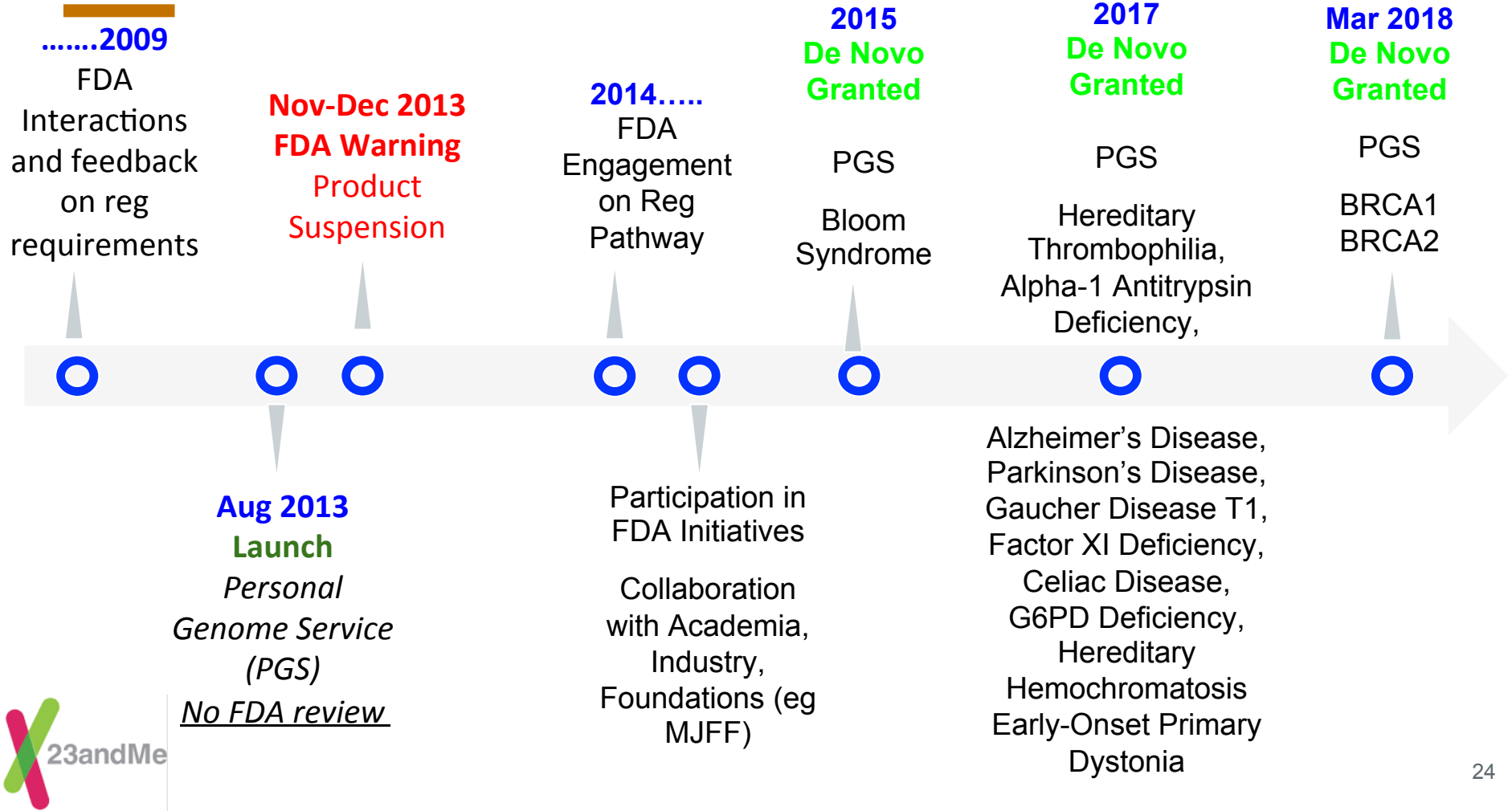
Differentiation

Small Business Case Study

FDA Partnership

Health + Ancestry Service

Get an even more comprehensive understanding of your genetics. Receive 75+ online reports on your ancestry, traits and health - and more. learn more


.....2009
FDA Interactions and feedback on reg requirements
Nov-Dec 2013
FDA Warning
Product Suspension
2014.....
FDA Engagement on Reg Pathway
2015
De Novo Granted
PGS
Bloom Syndrome
2017
De Novo Granted
PGS
Hereditary Thrombophilia, Alpha-1 Antitrypsin Deficiency,
Mar 2018
De Novo Granted
PGS
BRCA1
BRCA2
Aug 2013
Launch
Personal Genome Service (PGS)
No FDA review
Participation in FDA Initiatives
Collaboration with Academia, Industry, Foundations (eg MJFF)
Alzheimer's Disease, Parkinson's Disease, Gaucher Disease T1, Factor XI Deficiency, Celiac Disease, G6PD Deficiency, Hereditary Hemochromatosis Early-Onset Primary Dystonia

23andMe

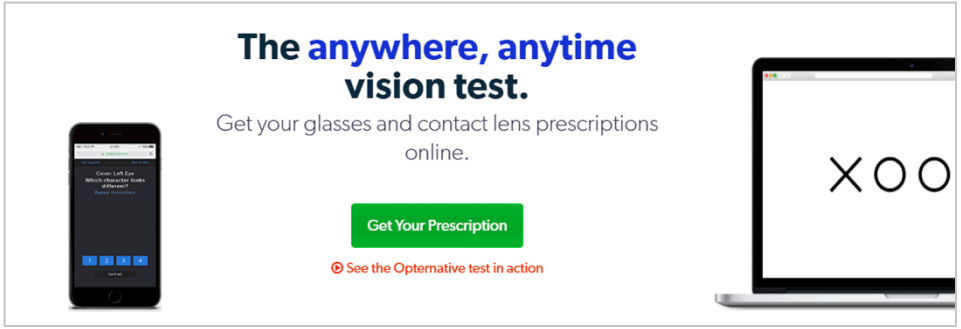
FDA Press Releases

Small Business Case Study

Lack of FDA Engagement

Opternative

WATCH



2016
FDA Formal Meeting

Office of Compliance

Office of Device Evaluation

Requirement of premarket submission to evaluate safety and effectiveness

Continued Marketing
Eye Exam Mobile Medical App

No FDA Submission
No FDA Registration and Listing

2017
FDA Warning
FDA review of website
Violations

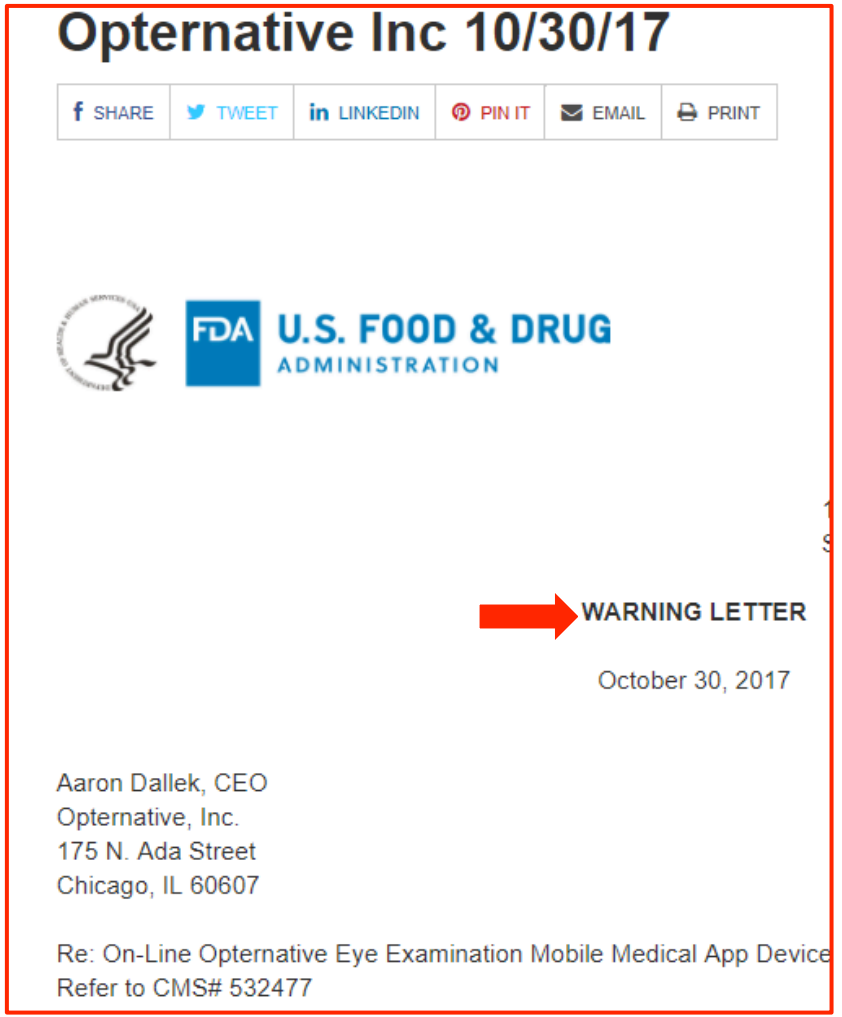
ADULTERATION: No approved application

MISBRANDING: No FDA notification of intent to commercialize

FDA ACTIONS: Seizure, injunction, civil money penalties…...

Opternative

FDA Letter Release, March 2018



Opternative Inc 10/30/17

SHARE | TWEET | LINKEDIN | PIN IT | EMAIL | PRINT

U.S. FOOD & DRUG ADMINISTRATION

WARNING LETTER

October 30, 2017

Aaron Dallek, CEO
Opternative, Inc.
175 N. Ada Street
Chicago, IL 60607

Re: On-Line Opternative Eye Examination Mobile Medical App Device
Refer to CMS# 532477

Small Business Case Study

FDA Engagement...but… Uncompetitive Product

Profile/Labeling

Analysts project blockbuster market

High % US population obese or overweight

2014
FDA Approval

LABEL Limitations

Require reduced-calorie diet + increased physical activity

Only 5-10% weight loss

Boxed Warning: Suicidal Thoughts; access limitations

Adverse effects (nausea); poor compliance

Poor uptake by patients, physicians, payers

Mar 2018
Orexigen files for bankruptcy

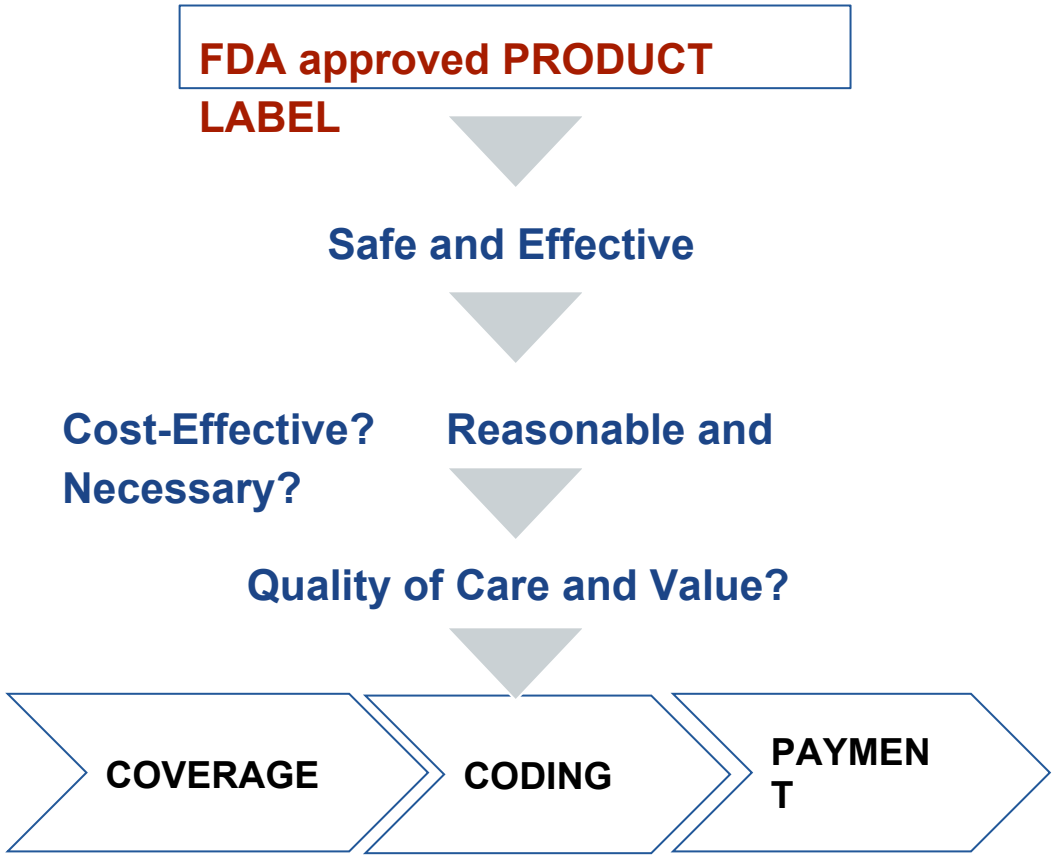
OREXIGEN THERAPEUTICS, INC. PLANS FOR NEAR-TERM SALE USING STRUCTURED PROCESS THROUGH CHAPTER 11 OF U.S. BANKRUPTCY CODE

OREXIGEN

Beyond First FDA Marketing Authorization

Patient Access

Reimbursement (Revenue, Return on Investment)

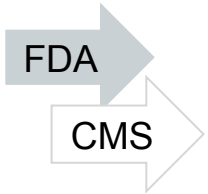


FDA vs CMS:

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

Obtain Payer Input on Development Program/Proposed Label simultaneously with FDA

Post-Marketing Experience

Safety profile
- Intended population
- Potentially other populations/Indications
- Safety issues
- Manufacturing issues

Real-World Evidence Patient, Physician, Caregiver
- New Tx approaches
- Regulatory decisions
- Coverage decisions
- Clinical practice decisions

Big Data Access and Analytics
- Advance benefit-risk assessment

AbiliLife
FDA Engagement and Product Roadmap

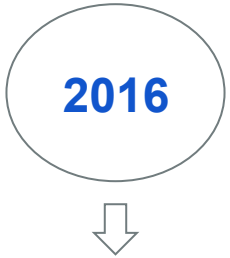
Label Development : Differences in wording impacting Evidentiary Requirements and Submission Strategy

Alert for High Fall Risk $$$

Versus

Prevention of Fall $$$$$$$$$$

Continuous FDA Engagement

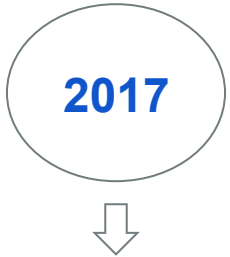


FDA Pre-Submission Meeting: Full portfolio

CMS Contact

Comment on draft FDA Guidance

Member, Coalition for Software guidances



Pre-Submission Supplement: Software Platform

Followup FDA T/Cs

Battelle/CMS contact on Quality Payment Strategies

FDA MDDT designation Submission

Pre-Submission Supplement: Portfolio, Life Cycle Optimization, Rare disease development

Parallel FDA-CMS feedback

Private Payer, VA engagement

2016 : AbiliLife Portfolio - BEFORE FDA Pre-Submission Meeting

- Medical Device Pathway: Traditional
- Options for off-the shelf software platform
- FDA assistance for CMS Engagement

2016: AbiliLife Portfolio- AFTER FDA Pre-Submission Meeting

- Optimized Portfolio Strategy
- Novel Medical Device pathway
- Potential FDA Designations for Platform
- Streamlined Strategies for Studies
- Facilitated Engagement with CMS
- Support for Grant Application

2017: FDA Pre-Submission Supplement Meeting on Software Platform

- Research Tool strategy
- Software Regulatory Needs and Strategic Options
- Support for Grant Application

2017-2018: Calibrace+ Post-Marketing Experience

CORE COMPENTENCIES

Calibrace+ Orthotic Back Brace for Spinal Disorders

- Certified durable medical equipment company (Board of Certification/ Accreditation)
- HCPCS codes L1310; L0650; L0651; L0648; L04574
- Utility Patent - Pending
- Clinical Trial - Pending
- National Science Foundation STTR grant Phase I

PAST PERFORMANCE

- Hospital Providers:
  - VA Denver Healthcare System
  - VA Philadelphia Healthcare System
  - VA Pittsburgh Healthcare System
- Insurance Providers
  - TriNet
  - Medicare
  - Blue Cross Blue Shield
  - Cigna

DIFFERENTIATORS

- Calibrace+ back brace engineered by AbiliLife
  - Provides upper torso support
  - Decreases fear of falling
  - Used for 600+ diagnosis codes
  - Made in America

ICD-10 code, L0457; eligible for use for over 600 diagnosis codes

Real-World Evidence

PORTFOLIO OPTIMIZATION

Calibrace+:

- Extension of population: Neuromuscular diseases
- Extension of indication: Lower back pain

Smart Calibrace

- Extension of population and subgroups
- Patient Reported Outcome endpoints meaningful to both FDA and CMS

2018: Patent Allowed Claims

Attorney Docket No. 0085022-000003

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	**PATENT APPLICATION**
Williamson, et al.	)	PHYSIOTHERAPEUTIC, AMBULATORY, AND MOBILITY VEST
Application No.: 14/728,138	)	
Filed: June 02, 2015	)	Group Art Unit: 3772
Confirmation No. 7702	)	Examiner: Lewis, Kim M.

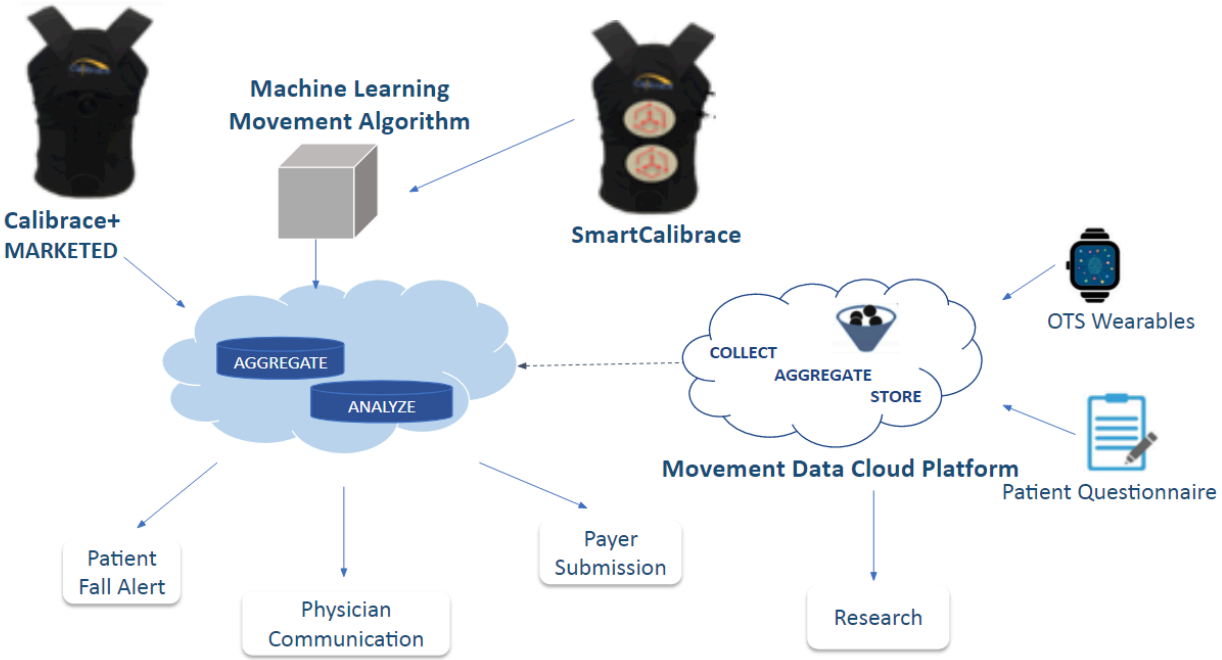
ALLOWED CLAIMS

PORTFOLIO OPTIMIZATION

Additional Device Description Claim:

Only back brace that improves posture and balance by lifting the shoulders up and back and giving entire back support

2018: AbiliLife Optimized Portfolio based on Post-Marketing Experience - FDA Pre-Submission Supplement Meeting



- Briefing Document in progress

Conclusions

Impact of FDA Engagement on

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

External Communications

Value Assessment of Portfolio

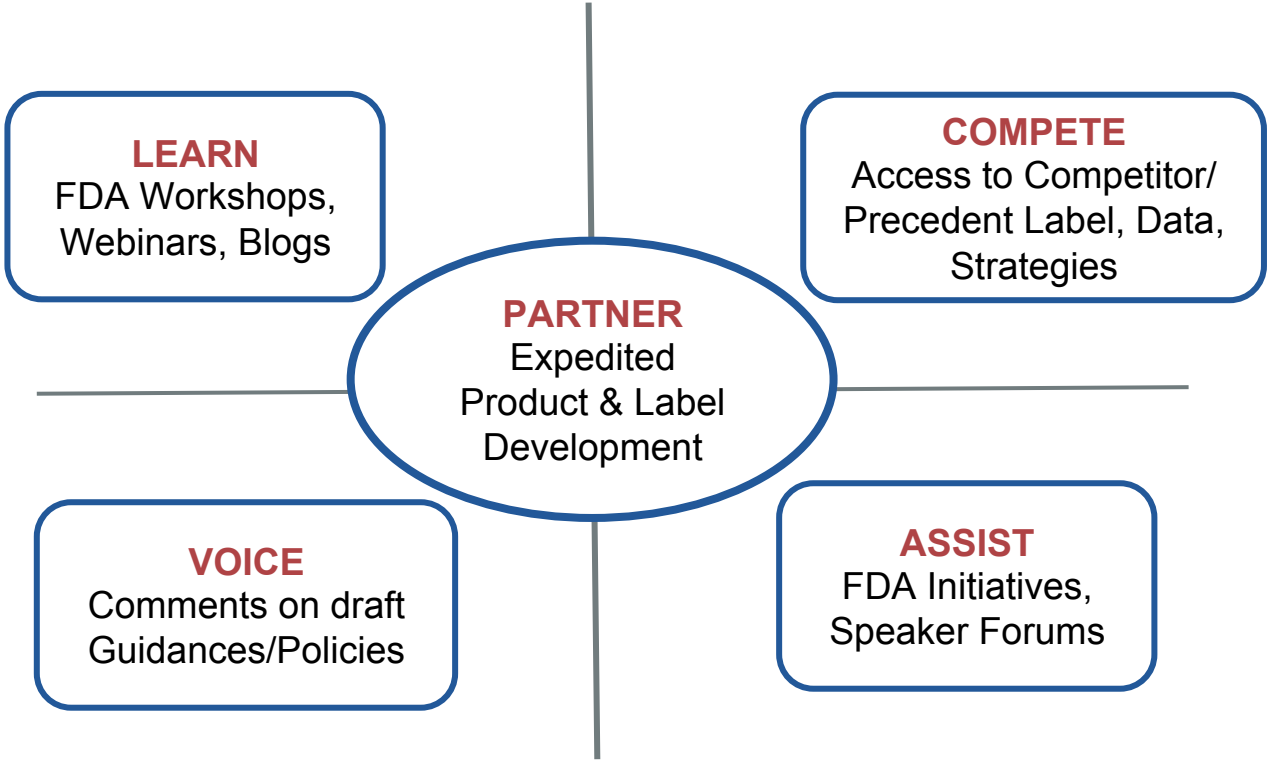
Portfolio Value Enhancement

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

BACKUPS

FDA is an Invaluable Resource



What is Benefit-Risk Framework

Benefit > Risk

Valid Scientific Evidence

Well-Controlled, Well Designed, Well Conducted,Well Documented, Qualified Experts

Totality of Evidence

Clinical, Non-clinical, Performance, Patient Perspectives, Post-Marketing, Novel Technology etc.)

DRUG

Ensure that the Benefits outweigh its Risks

- Analysis of Condition
- Current Treatment Options
- Benefit: Evidence, Uncertainties, Conclusions, Reasons
- Risk: Evidence, Uncertainties, Conclusions, Reasons
- Risk Management

DEVICE

Reasonable Assurance of Safety and Effectiveness (RASE)

- Benefit: Type, Magnitude, Probability, Duration
- Risks: Severity, Types, Number, Rates, Probability, Duration
- Other: Uncertainty, Patient Perspectives, Alternative Treatments, Risk mitigation, Post-market data, Novel Technology