FDA 101

Elora Gupta, PhD

Partner, Drug and Device Advisory Group

Based on my journey as a Pharmaceutical Scientist and Regulatory Scientist

Center For Innovation and Entrepreneurship
Carnegie Mellon University
April 13, 2016

My Journey

- **ACADEMIA** : ***Drug Development Principles and Clinical Assessment***
  - **Ohio State Unv.: PhD in Pharmaceutical Chemistry**
  - **Unv. Of Chicago: Post-Doctoral Fellow in Hem./Onc. clinical program**
  - **Cancer Institute of NJ : Disposition & Clinical assessment of new drugs**

- **INDUSTRY**: ***Drug & Device Development and Registration, Regulatory Sciences***
  - **Bristol-Myers Squibb, Otsuka, TransCelerate (non-profit)**
  - **Notable Drugs : Eliquis®, Avapro®, Sprycel®, Dacogen®, Busulfex®**
  - **Notable Devices : BreathTek®, MIND1**
  - **FDA Liaison**
  - **Global Regulatory Lead**
  - **Partnerships**

- **ADVISORY : *Drug and Device Advisory Group***
  - **Special Interest in Drug an Device Startups**
  - **Associated with CMU Startups**

Seminar Objective

Provide perspectives to facilitate

bridging

CMU-Research & Entrepreneurship in Medical Products

to

Patients, Physicians, Healthcare Providers

Drug, Device

- **D**iagnose
- **C**ure
- **M**itigate
- **T**reat
- **P**revent
- **S**tructure/ **F**unction of Organ
- No Chemical Action/ Metabolism (Device)

FDA

PROTECT & PROMOTE PUBLIC HEALTH

US DHHS Agency (Dept. of Health and Human Services)

ASSURE access to **SAFE, EFFECTIVE, HIGH-QUALITY** products

PROVIDE science-based information about the products

FACILITATE innovation

REGULATES

Today's seminar

FDA Classification : Drug and Device

- Small
- Molecules
- Biologics
- New Molecular Entities
- Generics
- Over The Counter (OTC)

✓NDA, sNDA
✓BLA, sBLA
✓ANDA

- General Controls (Class I)
- Special Controls (Class II)
- Life Supporting (Class III)

✓Exempt
✓Enforcement Discretion
✓510(k)
✓PMA, PDP
✓De Novo

Similar FDA Evaluation of Drugs and Devices

2016 FDA Perspectives

Robert Califf, MD
FDA Commissioner
Appointed: 2016

FDA

- Regulates 20% of nation's economy
- Makes enormous number of decisions every day
- Vital to the well-being of all Americans
- High-quality and impartial judgments—'*...despite the fact that many must ultimately disappoint (or at least not fully satisfy) one or more constituencies….*

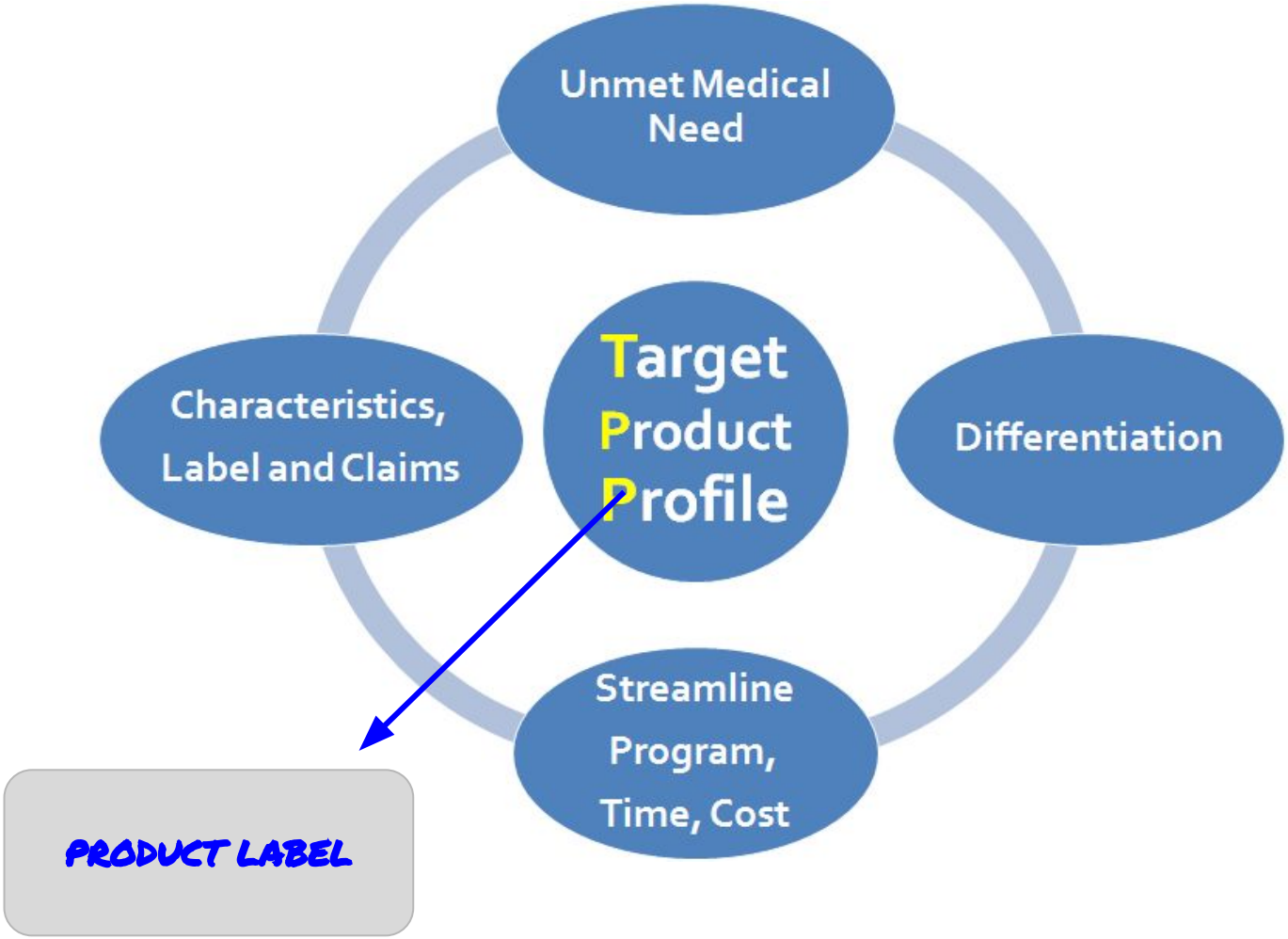
APPROVED PRODUCT LABELING

- Communicates product's **SAFETY & EFFECTIVENESS**
- Summarizes key **SCIENTIFIC INFORMATION**
  - Assess product's **RISK-BENEFIT** profile
  - Decide if product is **APPROPRIATE for PARTICULAR PATIENT**

Leah Christl, Ph.D
Office of New Drugs

Key Theme for Strategic Product Development

Begin with the end in mind...



Seminar Overview

STAKEHOLDERS

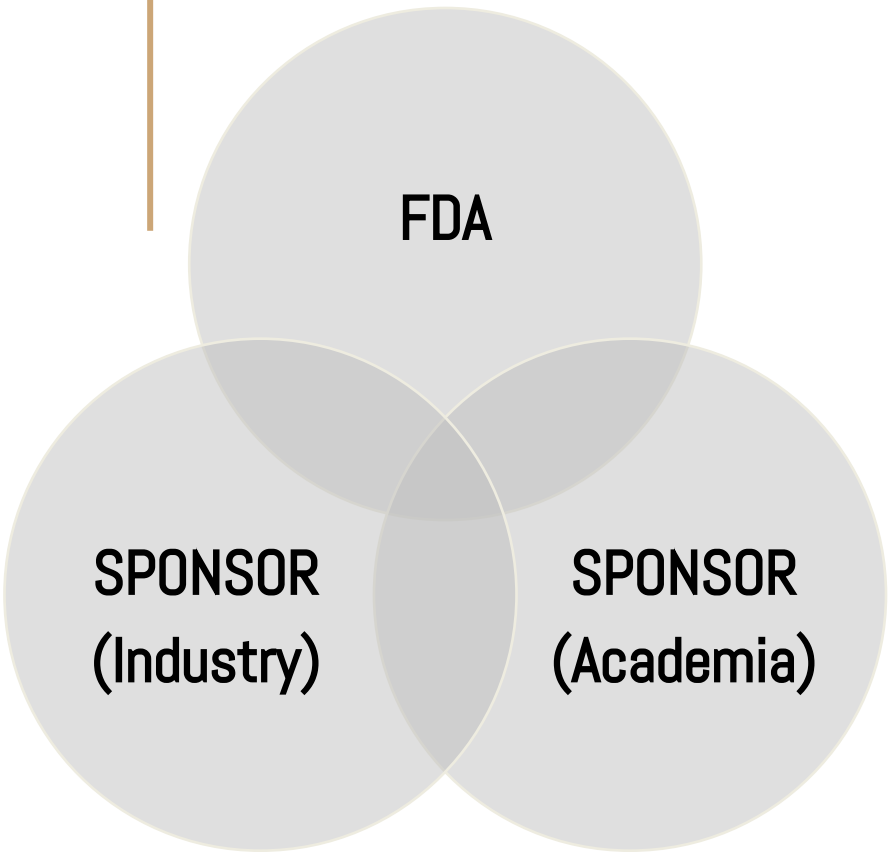
FDA

SPONSOR

Case Studies

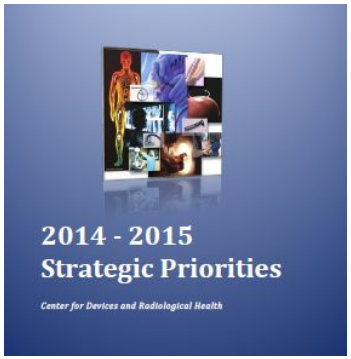
Learning Resources

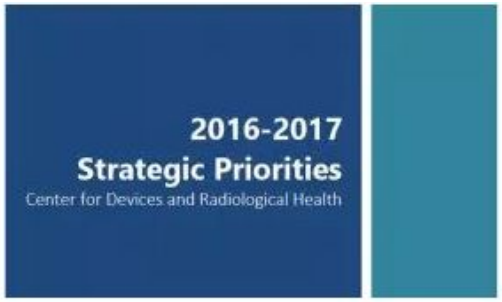
STAKEHOLDERS



FDA : '*Patients are at the heart of what we do*'

CDRH





CDER

FDA
Center for Drug Evaluation and Research (CDER)

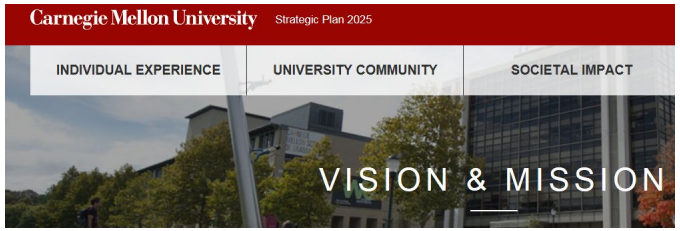
Strategic Plan 2013-2017

- **Availability, Quality, Integrity, Safe Use of Products**
- **Clinical Evaluation Modernization**
- **Regulatory Science Innovation**
- **Patient Voice**
- **Customer Service**

SPONSOR (INDUSTRY): Regulatory Strategy for Product Registration & Approval

- **Strategy** for Target Product Profile : Regulation + Science + Business
- **Voice** for Product Profile and Company to FDA

SPONSOR (ACADEMIA): Innovation & Advancement



To cultivate a transformative university community commit
(b) creating a collaborative environment open to the free e
entrepreneurship can flourish; and (c) ensuring individuals

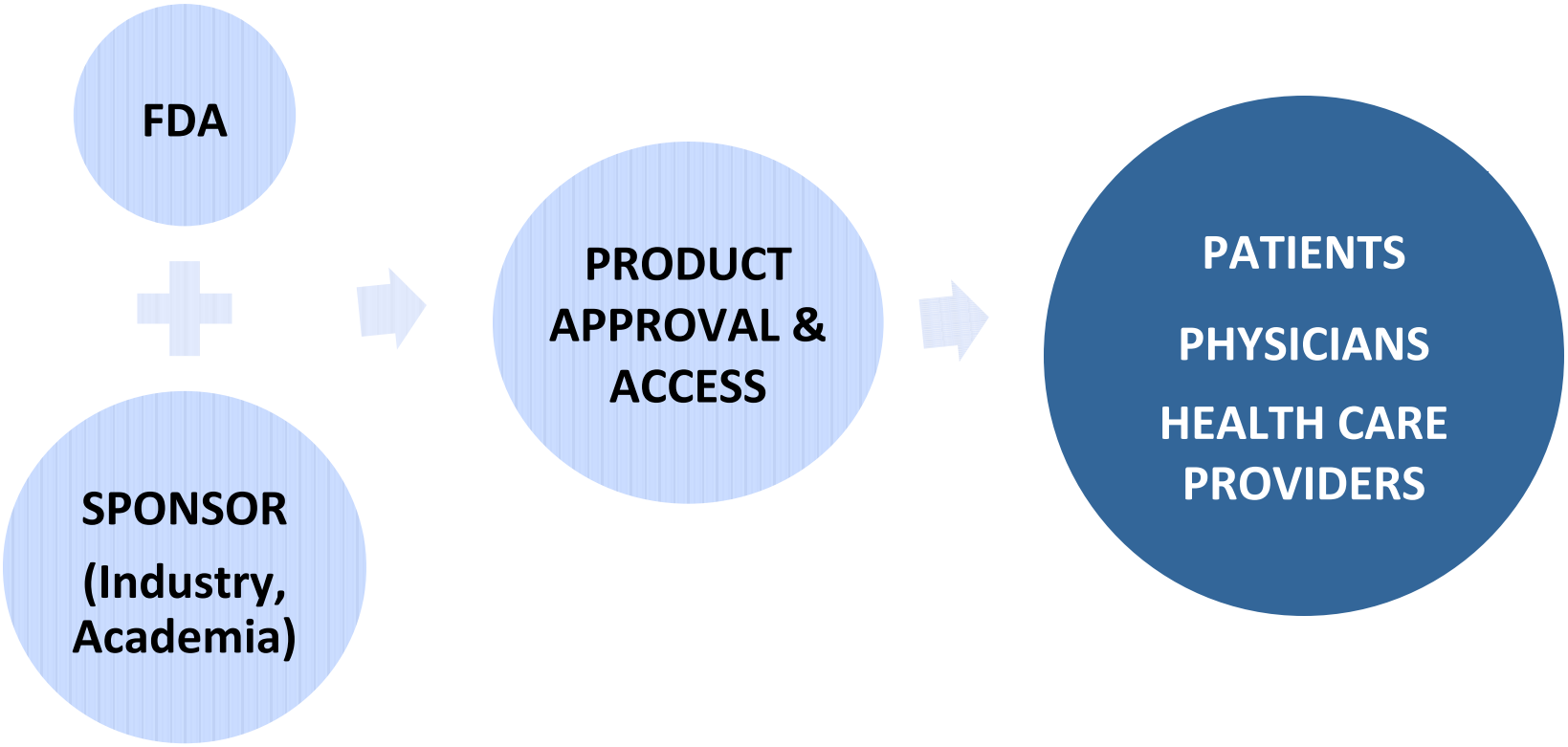
Carnegie Mellon University

Center for Innovation and Entrepreneurship

In the fall of 2012, the Carnegie Mellon Center for Innovation and Entrepreneurship (CIE) was created to strengthen and serve the already bustling culture of entrepreneurship and innovation at Carnegie Mellon, and to accelerate the commercialization of university research and innovative ideas.*

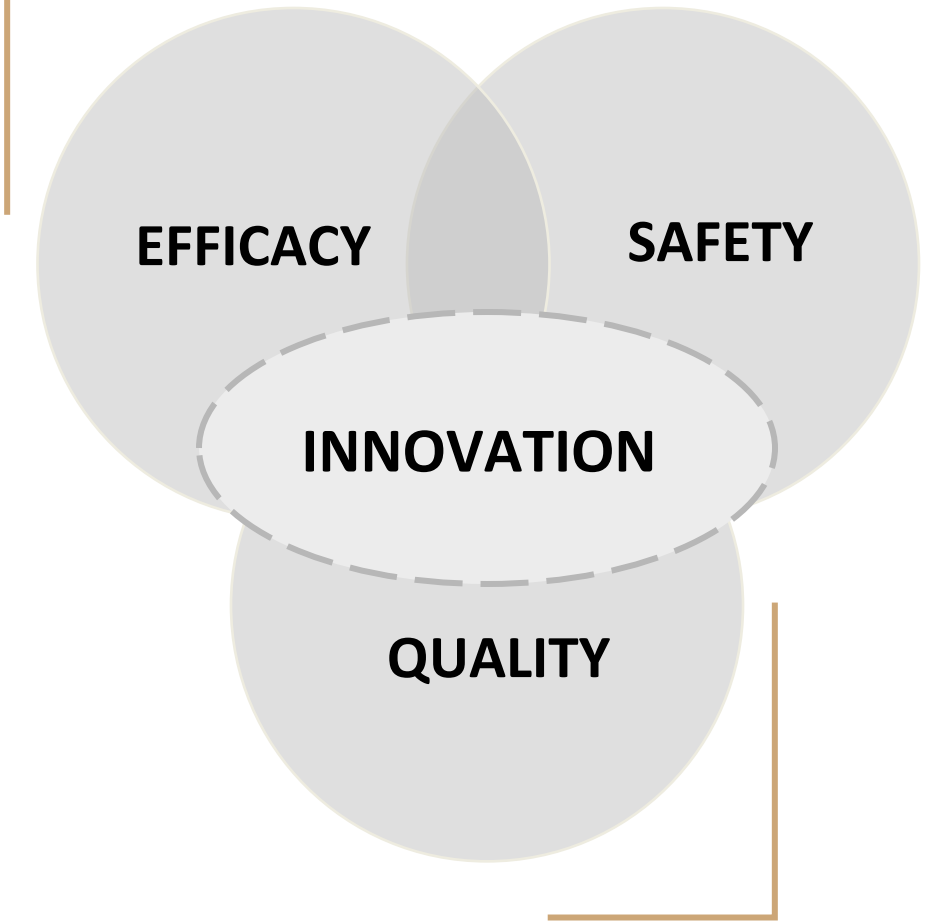
- Next - Gen medical products : Drugs and Devices
- Address Unmet Needs
- Define regulatory science standards for novel technologies

STAKEHOLDER SUMMARY : Shared Objective



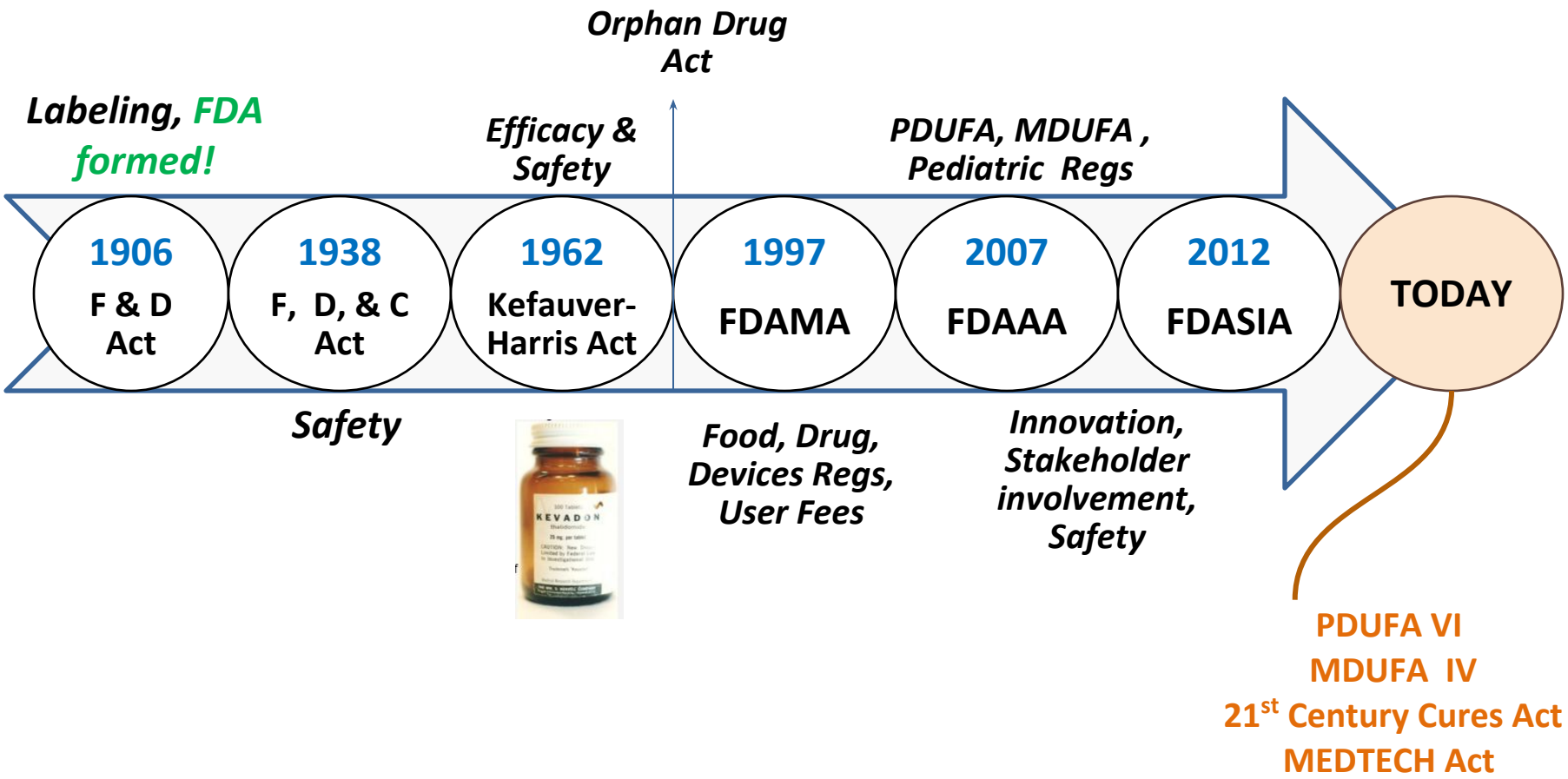
FDA QUOTE *"…….Ideally, Sponsors and FDA work collaboratively ….. having a shared public health goal of early availability of safe, effective, and high-quality (products) to the American public….. "*

FDA : Fundamentals



FDA's Evolution of Evidentiary Standards

http://www.fda.gov/AboutFDA/WhatWeDo/History/Milestones/ucm128305.htm



FDA's Communication of Evidentiary Stds

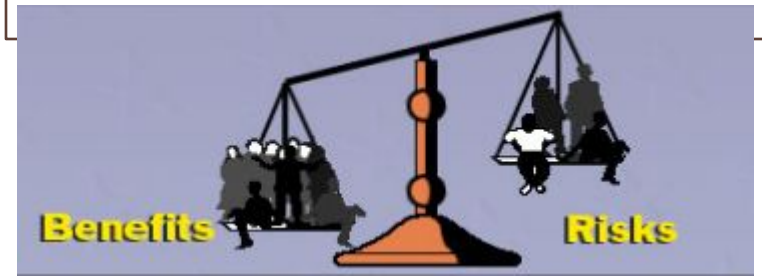
- **Code of Federal Regulations:** *Law*
  21CFR 200, 300s: Drugs, 21 CFR800s: Devices
- **Guidances :** *Recommendations*
- **Review Summaries (FOIA) :** *Assessment*
  Product approvals : NDA, 510(k), PMA summaries , Approved labels
- **Public Forums:** *Current Thinking, Feedback Seeking*
  Workshops, Advisory Committees, Patient Forums, Small Business Events
- **Alerts, Notifications, Social media :** *Real Time Communications*
  Safety, Recalls, Shortages, Inspection Findings

PROPRIETARY : Sponsor Submissions, Most Sponsor-FDA Communications, Negative Application Reviews

FDA Review Core Elements

B/R Framework

- **Benefit** : Type, Magnitude (clinically meaningful), Duration
- **Risk** : Adverse Event (severity, duration), Malfunction, Incorrect use , Cybersecurity
- **Quality:** Robustness of study design, conduct, analyses
- **Risk Management**
- Other:
  - *Unmet need*
  - *Patient Tolerance of risk, benefit perspective*
  - *Alternative treatments*
  - *Novel technology*



Labeling + Promotion

- Communicate ***Benefits and Risks*** and Information *for* ***Safe and Effective Use***
  - *Indication*
  - *Effectiveness, Safety*
  - *Prescribing Info. / Use Info.*
  - *Risk Management and Mitigation*
- All information **substantiated** by robust data and analyses
- **Key** for Product Branding & Differentiation based on 'Claims'
- **Basis** for Advertising and Promotion

FDA Review Core Elements

Quality and Compliance

- Codified by CFRs
- **Manufacturing**: cGMP
  - Quality Systems to meet specifications
- **Clinical** : GCP
  - Ethics, patient protection, quality of data collection and analyses
- **Laboratory**: GLP
  - Robustness of lab evaluations
- **FDA Inspections** : Pre-Approval, Post-Approval – *usually unannounced*
- Accountability : Sponsor (Senior Management)

Inspections, Compliance, Enforcement, and Criminal Investigations

Safety Surveillance

- From initiation of product development through lifetime
- Balance Pre- and Post-market
- **Sponsor Responsibilities**
  - Timely and Effective reporting (with causality assessment)
  - Safety Assessment Committee
  - Safety Surveillance Plan
- **FDA Impact Assessment**
  - Labeling
  - Product modifications
  - Guidances
  - Notifications, Recall

The FDA Recommends Against Using OxySure Portable Emergency Oxygen System, Model 615: FDA Safety Communication

FDA Interactions

Sponsor Meetings

- **Collaboration** on product development
- From product inception to lifetime
- **Timely and effective**
- **Gain alignment** on scientific and regulatory issues
- Several types , Free
- **Sponsor Advantage**: Minimize time/resource waste, optimize product profile
- **FDA Advantage**: View spectrum across sponsors, provide advice while upholding confidentiality

Global Considerations

- Alignment on **technical requirements**

Drugs : **ICH** (International Conference on Harmonisation

Devices : **IMDRF** (International Medical Device Regulators Forum)

- International **Inspections**: GMP, GCP, GLP
  - Products intended for US
  - Compliance with US law and regulations

Updated: FDA Bans Imports From Singapore Device Firm After Inspection Refused

Posted 18 January 2016

FDA Opportunities

Expedited Development and Review

- **Life threatening, irreversibly debilitating** diseases/conditions
  - **Drugs**: *Fast Track, Priority Review, Breakthrough , Accelerated Approval, Expanded Access*
  - **Devices**: *Expedited Access, Priority Review*
- **Rare diseases**
  - Orphan Designation (<200,000)
  - Humanitarian Use (<4,000)
  - Financial incentives
- Incentives
  - Neglected Tropical Disease
  - Qualified Infectious Disease Product

Small Business Outreach Vendor Fair

Small Business Support

- Outreach Fair
- **Vendor** contracts
- **Grants**
- Business Investments
- Technology Transfer
- Learning Workshops
- **User Fee waiver/reduction**

Doing Business With FDA

FDA Innovation

Leveraging 'Big' Data

- Utilizing human genome sequence & clinical trials databases
- Informatics capabilities, IT/software tools

Patient-Focused Drug Development

Public Meeting on Patient-Focused Drug Development for Huntington's and Parkinson's Diseases

Patient Reported Outcomes

- Patients' input on specific disease areas, impact on daily life
- Include in product development, develop and validate

PrecisionFDA

precisionFDA

- Community-generated content, cloud-based platform
- In response to President Obama's 'Precision Medicine' initiative
- Ensure that genomic tests provide reliable and accurate results

FDA Innovation


Digital Health

Digital Health

- Functionality focused oversight, promote innovation, patient engagement and Safety
- **Medical Device Data Systems** (**MDDS**- transfer, storage, display) : From CIII to CI
- **Mobile Medical Apps** : Risk Based - Regulated, Enforcement Discretion, Not Regulated
- **Device Accessories** : Risk based classification
- **General Wellness Apps** : Low risk
- **Clinical Decision Software (CDS)**: Guidance to be developed
- NEW **FTC Mobile Health Apps Interactive Tool**

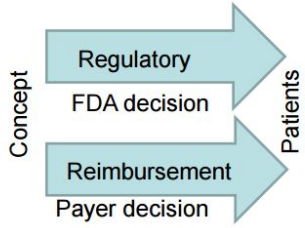
Cybersecurity

- Public health issue
- **Premarket Development Guidance** : Device Design, Vulnerability, Management
- **Postmarket Management Guidance:** Collaborative Risk-Based,Identify, Protect, Detect, Response, Recover
- Information Sharing and Analysis Organizations (ISAO)

FDA

HH-ISAC

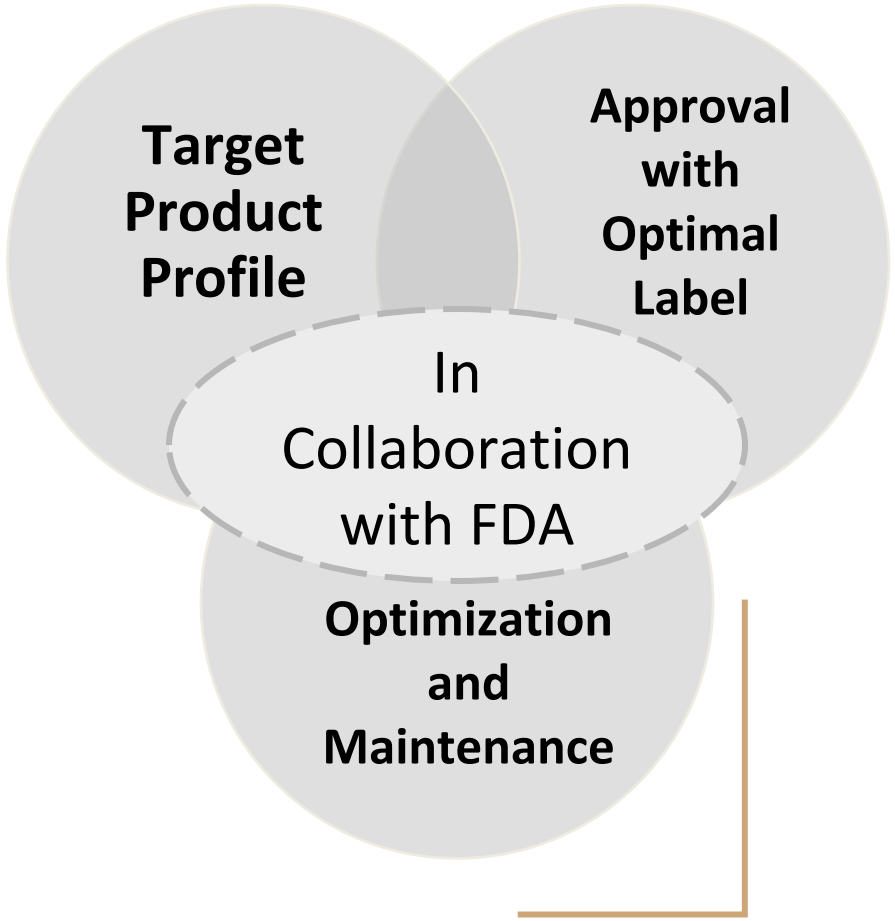
FDA Innovation



Pricing + Reimbursement

- Pricing NOT FDA purview
- Device voluntary pilot program : **FDA-CMS Parallel Pilot Project (2011-2015); 2016 notice**
- Concurrent review to reduce time between FDA's approval and Medicare coverage
- Cologuard®
  - Parallel FDA and CMS meetings to align on development program (n>10,000 pts)
  - Parallel FDA and CMS reviews
  - FDA approval and CMS proposed national coverage the same day !

Industry : Regulatory Strategy



Regulatory Plan :A Dynamic Document for Target Product Profile

FDA Partnership : Voice of Product & Sponsor

- **Product**
  - Aligning on Product Profile
  - Accurate, balanced , timely information
  - Effective FDA Meeting Management
- **Presentation**
  - **Private** : 1 on 1 FDA-Sponsor
  - **Public** : Advisory Committee next slide
- **Policy**
  - Guidance/Policy review and comment
  - Speaker in FDA Workshops
  - Speaker in External Forums
  - Publications

View of the Dec. 20, 2012 Meeting of the Arthritis Advisory Committee

FDA
ADVISORY COMMITTEE MEETING

CASE STUDIES

Importance of prospective Target Product Profile Strategy and FDA Alignment

Pharma

Biotech

Entrepreneur

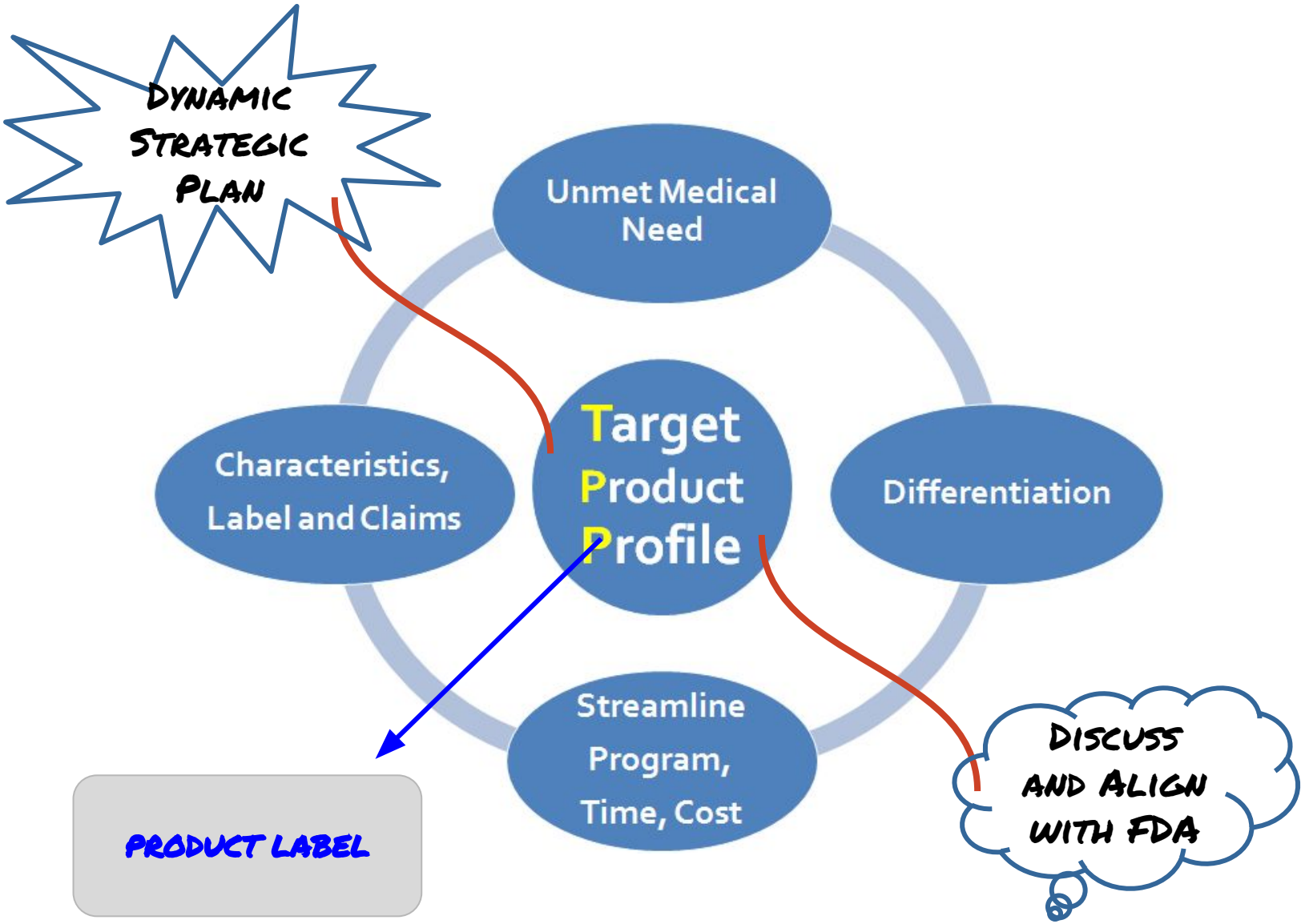
Academia

Novel Technology

Product Optimization

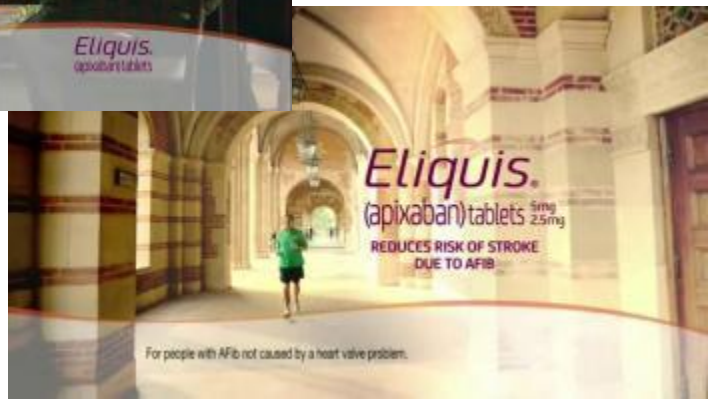
Key Theme for Strategic Product Development

Begin with the end in mind...



Pharma

Approved for several indications

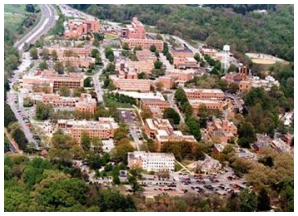


For Hip & Knee Replacement Surgery Patients

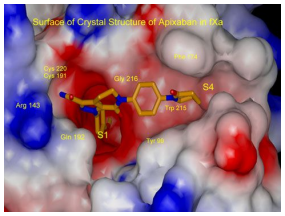
For Patients with Atrial Fibrillation (AFib) Not Caused by a Heart Valve Problem

For Deep Vein Thrombosis (DVT) & Pulmonary Embolism (PE) Patients

Alliance to address unmet need to replace warfarin



Birth : Dupont January 10th, 2000



Tight binding to FXa, coagulation factor

Acquired by Bristol-Myers Squibb, 2001

Alliance with Pfizer, 2007

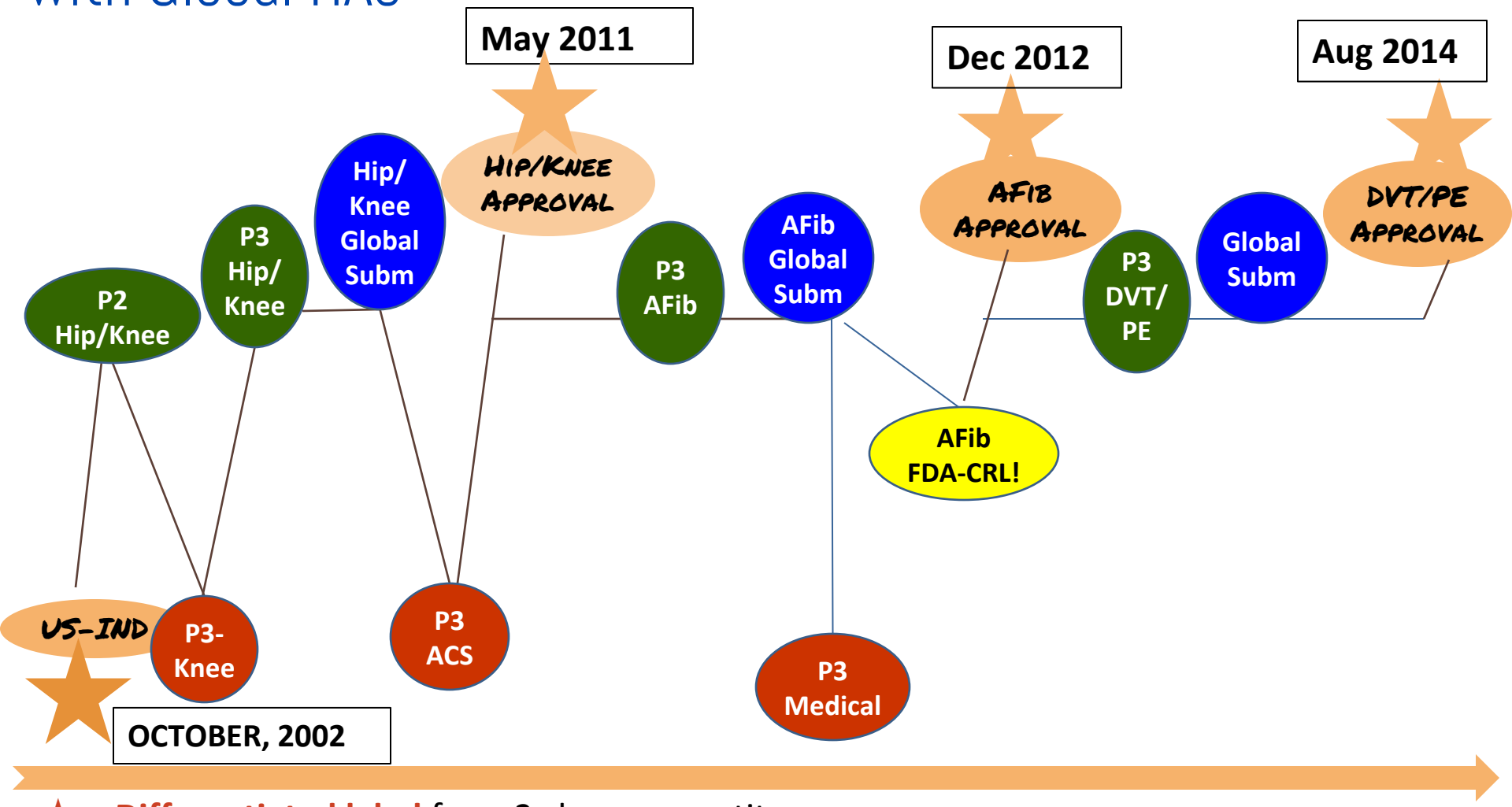
> 60,000 subjects, Exposures : 20 days - ~ 2 yrs, Dose range 2.5 – 10 mg BID

EXPANSE

Hip/Knee Surgery	AFib	DVT/PE	ACS	Medical
ADVANCE-1 ADVANCE-2 ADVANCE-3	ARISTOTLE AVERROES	AMPLIFY AMPLIFY-EXT	APPRAISE-2	ADOPT

DVT: Deep Vein Thrombosis
PE: Pulmonary Embolism
ACS : Acute Coronary Syndrome

LEARNINGS: Persistence/Partnership through Peaks & Troughs, Variations in Global HA Standards, Alignment with Global HAs



★ **Differentiated label** from 2 close competitors

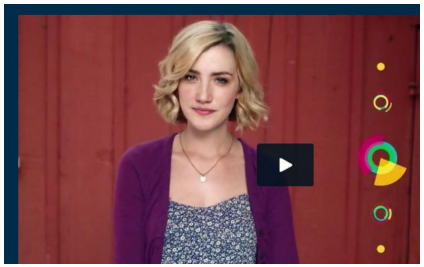
★ **Simultaneous** Global Submission Plan included 100+ countries

★ **Global HA Engagement** F2F Meetings with >20 Agencies ; 100s responses to queries

! CRL : Complete Response Letter

Biotech

Innovative technology associated with single-nucleotide polymorphism



2013 Ad

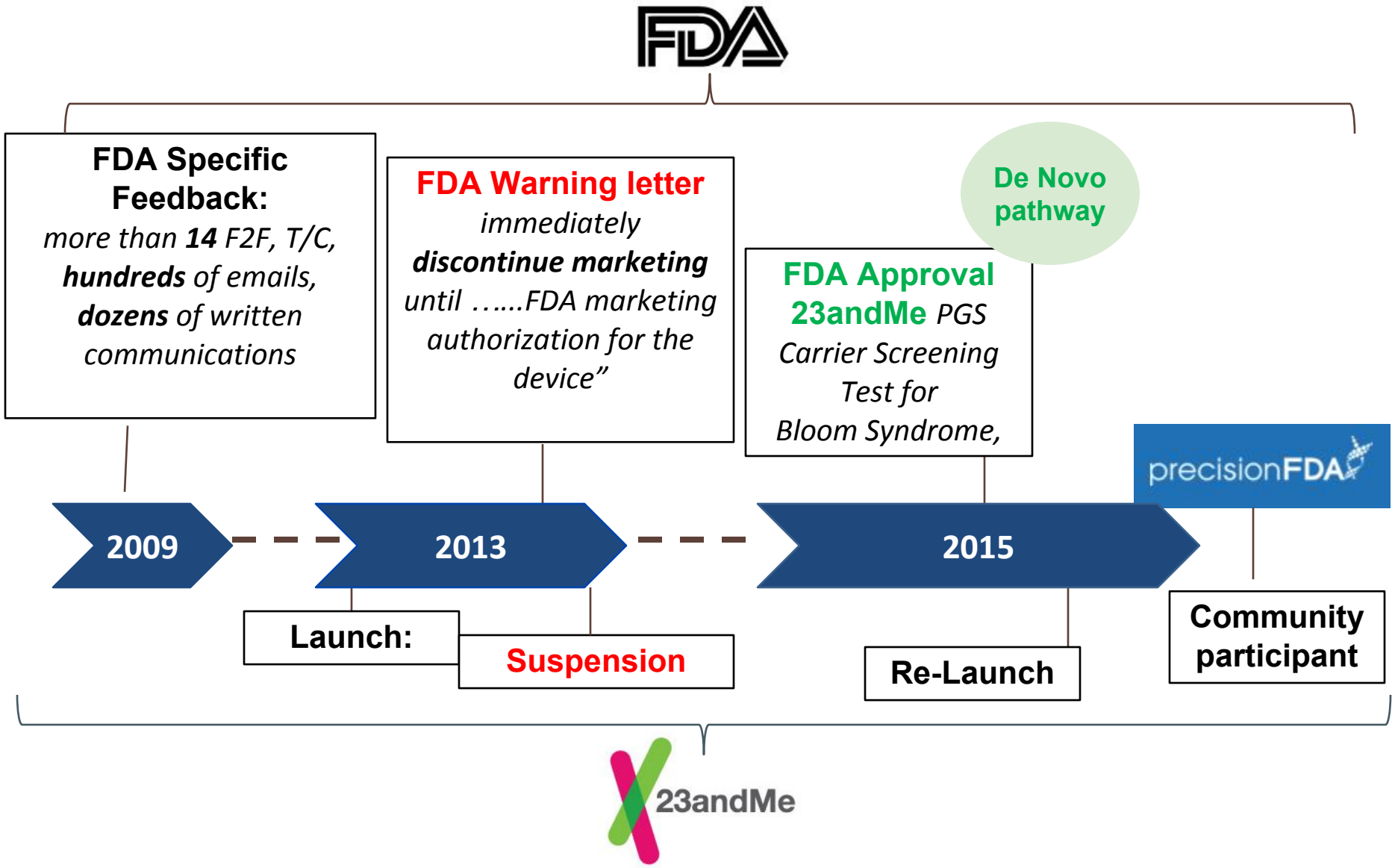
Personal Genome Service *(PGS) learn "**increased risk of heart disease, arthritis, gallstones**…."*.

2016 Ad

*……Reports meeting FDA standards,…**health, traits, ancestry**…."*.

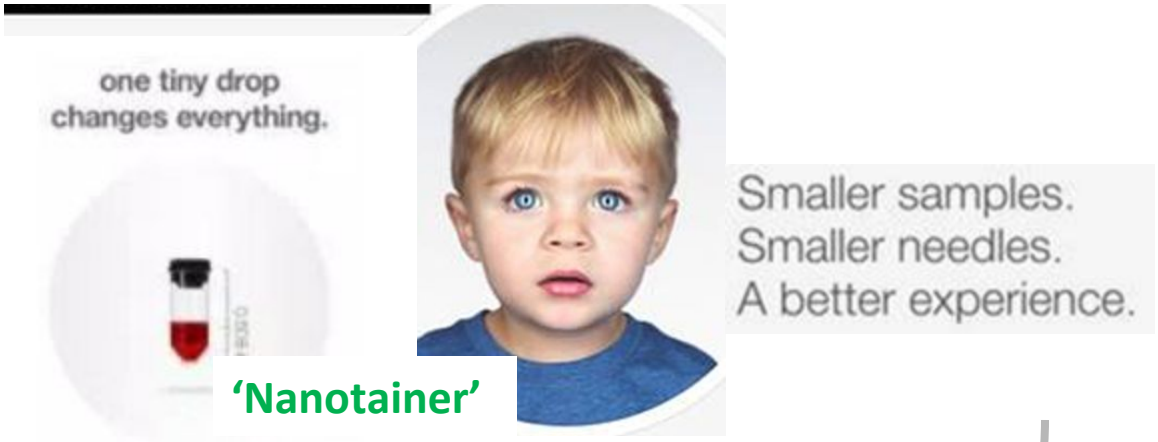
URLs:
https://www.youtube.com/watch?v=LrtPoke4X2g
https://www.youtube.com/watch?v=zeo7zPzZwIk

LEARNINGS: Address FDA Stds, Gain Alignment, Approval & Continue Partnership



Entrepreneur

Novel concept – but scientific validity?



'Nanotainer'

December 2015, FDA

U.S. Probes Theranos Complaints

Blood-testing startup's practices investigated over concerns about acc

January 2016, CMS

FEDERAL REGULATORS SAY A THERANOS LAB HAS SERIOUS PROBLEMS

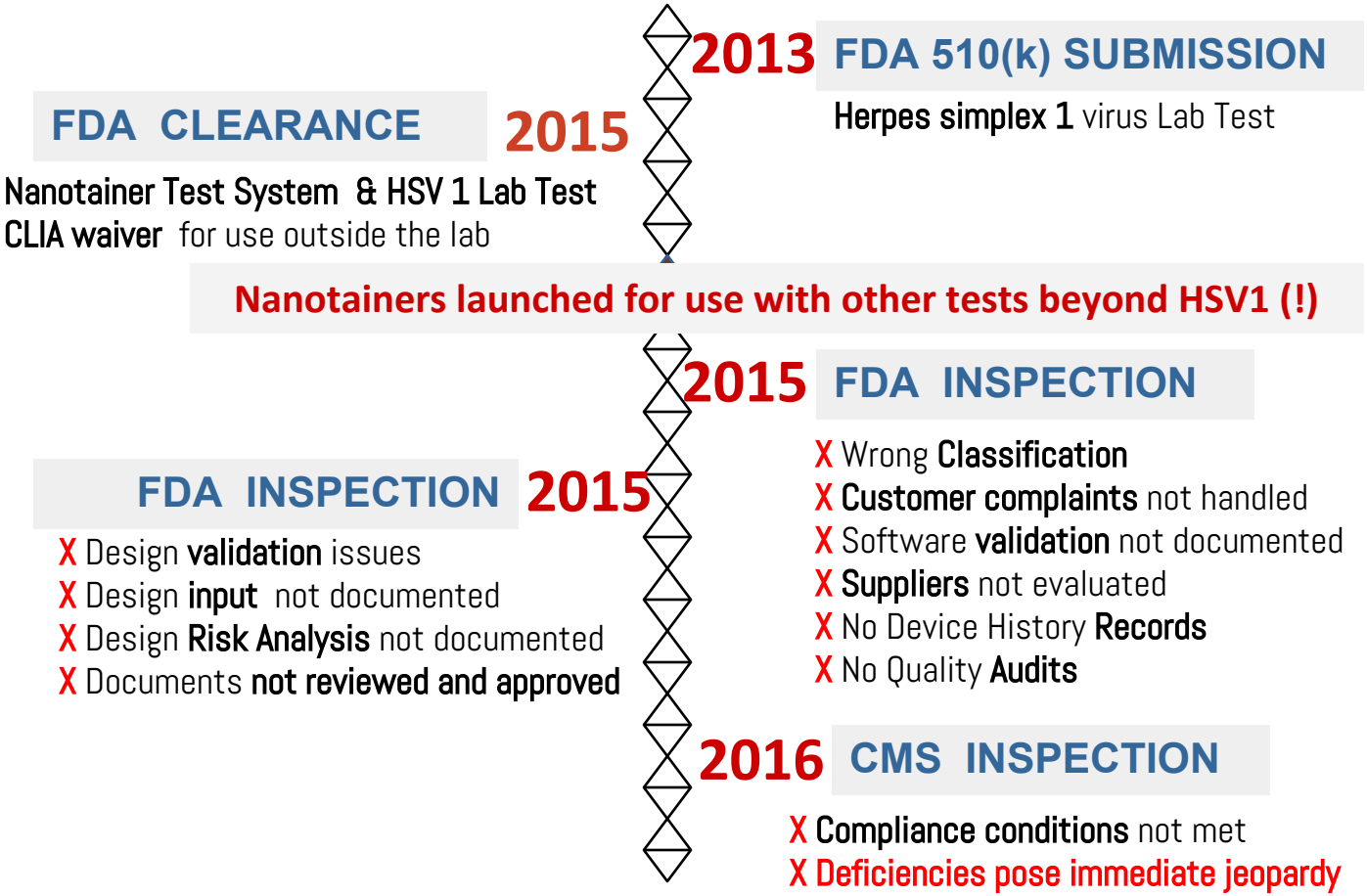
Theranos blood testing inconsistent with other labs, study shows

March 2016, Journal of Clinical Investigation

Evaluation of direct-to-consumer low-volume lab tests in healthy adults

Brian A. Kidd,[1,2,3] Gabriel Hoffman,[1,2] Noah Zimmerman,[3] Li Li,[1,2,3] Joseph W. Morgan,[3] Patricia K. Glowe,[1,2,3] Gregory J. Botwin,[3] Samir Parekh,[4] Nikolina Babic,[5] Matthew W. Doust,[6] Gregory B. Stock,[1,2,3] Eric E. Schadt,[1,2] and Joel T. Dudley[1,2,3]

LEARNINGS: Gaps in Reg Strategy, Design Validation and Quality, Safety measures…….



STOP using nanotainers
WITHDRAW contracts : Walgreens & Safeway
SUBMISSION to FDA for other tests
RESPOND to FDA and CMS Deficiencies

Academia

Northwestern Medicine®

Edwards Lifesciences

LEARNINGS: Gaps in Understanding/Implementing FDA Stds, Academic Responsibility, Patient Safety

"Myxo"Mitral Annuloplasty Ring invented by surgeon

Not cleared by FDA - Experimental device

2006
Used in surgery without informed consent, no FDA communication

2008/2009
FDA 510(k) submission and clearance by mnf (Edwards Lifesciences)

Caused ST-elevation MI during the implantation procedure, subsequent heart failures

FROM SURGERY TO SENATE: THE MYXO RING CASE

2008 - TODAY

- FDA Warnings
- Senate Investigation
- Patient Lawsuits
- Market Removal

Novel Technology

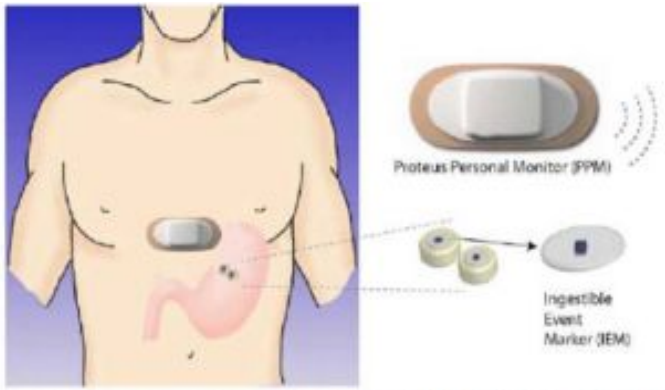
Otsuka

+

MIND1

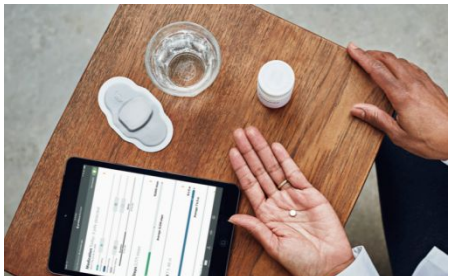
proteus
DIGITAL HEALTH

Novel Approach to Medication Adherence



Integrated System:

1) FDA-approved medication (ABILIFY®)
2) Sensor within the medication tablet (the Proteus ingestible sensor)
3) Measure actual medication-taking patterns and physiologic response
4) Communicated to the patient
5) Communicated to the patient's physician and/or caregiver (with patient consent)



10 SEPTEMBER, 2015

U.S. FDA Accepts First Digital Medicine New Drug Application for Otsuka and Proteus Digital Health

LEARNINGS: Setting Regulatory Precedence, Rapid Adoption of Evolving Guidances, Novel submission & Labeling

Proteus Ingestible Sensor Approval : De Novo Pathway

Proteus-Otsuka Alliance : 'Digital Medicine' combining ABILIFY with Proteus Sensor

Designated Combination Product - No Precedent
Managing CDER and CDRH interactions

Continuum of New Guidances - Mobile Medical Apps, Cybersecurity, Human Factor Testing, Packaging, Software Change Management

NDA Submitted: Proposed Novel Indication and Labeling developed in Alliance with CDER/CDRH

OPTIMAL PRODUCT PROFILE

LEARNINGS: Gaps in Precedent Analysis, Differentiation, Addressing Patient & Physician Needs

2006 — **FDA APPROVAL**

- Technological Advance
- No need for injections
- Lung Safety Concerns *in label*
- *Lung Safety Tests prior to prescribing*
- Teach inhaler use *due to novel mechanism*

EXUBERA

2007 — **MARKET WITHDRAWAL**

- Poor sales
- Physician concern: Safety, cumbersome patient training
- Patient concern: Large size, embarrassing to use in public

Insulin Flop Costs Pfizer $2.8 Billion

2015 — **FDA APPROVAL**

- Small size
- Lung Safety Concerns
- Spirometer tests

afrezza

2016 — **MARKET?**

MannKind Afrezza Sales Flop Again, Sanofi Losing Patience

MannKind Is On Its Way To Bankruptcy - Are Executives Jumping This Sinking Ship?

Back in control of Afrezza, MannKind refocuses on endocrinologists to give launch a jolt

LEARNING RESOURCES

FDA Learning is a click away

Public Meetings at the FDA White Oak Campus

WEBINARS, WORKSHOPS

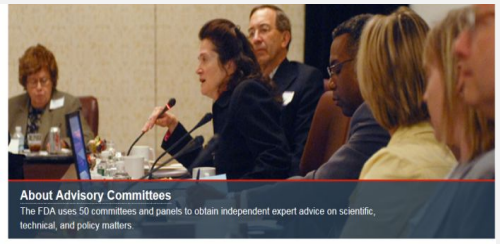
Join remotely ..or attend in person to network

INFORMATION, SUBSCRIPTIONS

Current Information updates

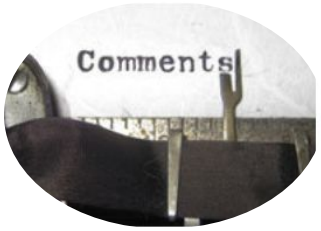
ADVISORY COMMITTEE MEETINGS

Insights into FDA, Medical Community, Consumer views



Advisory Committee Calendar

Let your voice be heard by FDA



GUIDANCES

Postmarket Management of Cybersecurity in Medical Devices

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

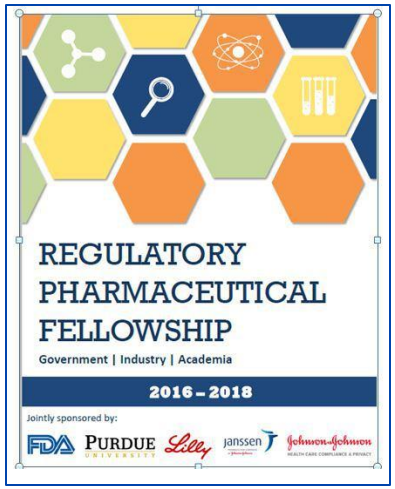
Document issued on: January 22, 2016

You should submit comments and suggestions regarding this draft document within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

LEGISLATION

Patient and Consumer Stakeholder Meetings - MDUFA Reauthorization, 2015-2016

Many Ways Engage with FDA



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Posted on October 22, 2015 by FDA Voice

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EXTERNAL SOURCES: Newsfeeds, Blogs, Organizations

- **Drug, Device News** : Development & Regulatory
  - FirstWord, MedGadget,MobiHealth News, RF Today
- **My Blog** : Drug and Device Digest http: //druganddevicedigest.com/
- **Societies, Trade Organizations, Conferences**:
  - Reg. Affairs Professional Society (RAPS)
  - Drug Information Association (DIA)
  - Trade Organization : PhRMA, AdvaMed, MDMA

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