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 and 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

FDA

- Diagnose
- Cure
- Mitigate
- Treat
- Prevent
- Structure/Function of Organ
- No Chemical Action/Metabolism (Device)

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

http://www.fda.gov/

Today’s seminar
FDA Classification: Drug and Device

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

- 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

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....

Robert Califf, MD
FDA Commissioner
Appointed: 2016

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...

- Unmet Medical Need
- Characteristics, Label and Claims
- Differentiation
- Streamline Program, Time, Cost

PRODUCT LABEL
Seminar Overview

STAKEHOLDERS

FDA

SPONSOR

Case Studies

LEARNING RESOURCES
STAKEHOLDERS

FDA

SPONSOR (Industry)

SPONSOR (Academia)
FDA: ‘Patients are at the heart of what we do’

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

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
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

- Efficacy
- Safety
- Innovation
- Quality
FDA’s Evolution of Evidentiary Standards

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

Labeling, FDA formed!

1906 F & D Act

1938 F, D, & C Act

1962 Kefauver-Harris Act

1997 FDAMA

2007 FDAAA

2012 FDASIA

Orphan Drug Act

Efficacy & Safety

PDUFA, MDUFA, Pediatric Regs

Food, Drug, Devices Regs, User Fees

Innovation, Stakeholder involvement, Safety

Safety

TODAY

PDUFA VI

MDUFA IV

21st Century Cures Act

MEDTECH Act
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
**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

**FDA Review Core Elements**

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**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
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)

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
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
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

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FDA Opportunities

Small Business Outreach Vendor Fair

**Small Business Support**

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

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**Doing Business With FDA**
**Leveraging ‘Big’ Data**
- Utilizing human genome sequence & clinical trials databases
- Informatics capabilities, IT/software tools

**Patient Reported Outcomes**
- Patients’ input on specific disease areas, impact on daily life
- Include in product development, develop and validate

**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
**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)
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!

COLON CANCER SCREENING made easy, WITH NONINVASIVE COLOGUARD®

Yes, COLOGUARD IS COVERED BY MEDICARE.
INDUSTRY: REGULATORY STRATEGY

- Target Product Profile
- Approval with Optimal Label
- In Collaboration with FDA
- Optimization and Maintenance

Product Optimization and Maintenance with Approval in Collaboration with FDA
Regulatory Plan: A Dynamic Document for Target Product Profile

**START EARLY** – Discovery/ Specification stage

**DEFINE** : Optimum Profile

**PROPOSED LABEL** : Indication, Claims, Supporting data

**DEVELOPMENT PROGRAM** : To support proposed label

**REG. INTELLIGENCE** : Guidances, Precedents, Competition

**FDA PARTNERSHIP** : Discuss/Align on program, label

**EXPEDITED, INNOVATION OPTIONS** : Evaluate

**SMALL BUSINESS STRATEGY** : Evaluate opportunities

**SUBMISSION STRATEGY** : Content and Requirements

**INSPECTION READINESS** : Pre- and Post-Approval

**PROMOTION COMPLIANCE** : Based on Approved label

**SAFETY MONITORING** : Pre- and Post-Approval

**GAPS & MITIGATION** : Continual assessment

**LIFE CYCLE OPTIMIZATION** : Proactive disc. with regulators

**GLOBAL STRATEGY** : Simultaneous or sequential launch
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

- **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
Importance of prospective Target Product Profile Strategy and FDA Alignment

CASE STUDIES

Pharma

Entrepreneur

Biotech

Academia

Novel Technology

Product Optimization
Key Theme for Strategic Product Development

Begin with the end in mind...

Dynamic Strategic Plan

- Unmet Medical Need
- Characteristics, Label, and Claims
- Streamline Program, Time, Cost
- Differentiation
- Discuss and Align with FDA

PRODUCT LABEL
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

- **Hip/Knee Surgery**
- **AFib**
- **DVT/PE**
- **ACS**
- **Medical**

**Legend:**

- **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

P2 Hip/Knee
P3 Hip/Knee Global Subm
Hip/Knee Approval
May 2011

P3 ACS
P3 AFib
P3 Global Subm
AFib Approval
Dec 2012

P3 DVT/PE
P3 Global Subm
Global Subm
DVT/PE Approval
Aug 2014

US-IND
P3 Knee
P3- Knee

★ CRL : Complete Response Letter
Innovative technology associated with single-nucleotide polymorphism

Personal Genome Service (PGS) learn “increased risk of heart disease, arthritis, gallstones ....”.

......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

FDA Specific Feedback:
more than 14 F2F, T/C, hundreds of emails, dozens of written communications

FDA Warning letter immediately discontinue marketing until …..FDA marketing authorization for the device”

FDA Approval 23andMe PGS Carrier Screening Test for Bloom Syndrome,

2009
Launch:

2013
Suspension

2015
Re-Launch

Community participant

De Novo pathway
Entrepreneur
Novel concept – but scientific validity?

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

March 2016, Journal of Clinical Investigation

Theranos blood testing inconsistent with other labs study shows

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

Brian A. Kidd,1,2,4 Gabriel Hoffman,1,2 Noah Zimmerman,2 Li Li,1,2,4 Joseph W. Morgan,2 Patricia K. Glowe,1,2,4 Gregory J. Botwin,2 Samir Parekh,5 Nikolina Babic,5 Matthew W. Doust,5 Gregory B. Stock,1,2,4 Eric E. Schadt,1,2 and Joel T. Dudley1,2,4
LEARNINGS: Gaps in Reg Strategy, Design Validation and Quality, Safety measures…….

**FDA CLEARANCE**
- 2015
  - Nanotainer Test System & HSV 1 Lab Test
  - CLIA waiver for use outside the lab

**FDA INSPECTION**
- 2015
  - Design validation issues
  - Design input not documented
  - Design Risk Analysis not documented
  - Documents not reviewed and approved

**2013 FDA 510(k) SUBMISSION**
- Herpes simplex 1 virus Lab Test

**2015**
- Nanotainers launched for use with other tests beyond HSV1 (!)

**2015 FDA INSPECTION**
- X Wrong Classification
- X Customer complaints not handled
- X Software validation not documented
- X Suppliers not evaluated
- X No Device History Records
- X No Quality Audits

**2016 CMS INSPECTION**
- X Compliance conditions not met
- X Deficiencies pose immediate jeopardy

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

EXUBERA

afrezza
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

2007
- MARKET WITHDRAWAL
  - Poor sales
  - **Physician concern:** Safety, cumbersome patient training
  - **Patient concern:** Large size, embarrassing to use in public

2015
- FDA APPROVAL
  - Small size
  - Lung Safety Concerns
  - Spirometer tests

2016
- MARKET?
  - MannKind Afrezza Sales Flop Again, Sanofi Losing Patience
  - MannKind Is On Its Way To Bankruptcy - Are Executives Jumping This Sinking Ship?

Insulin Flop Costs Pfizer $2.8 Billion
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

Subscriber Services: Manage Preferences | Unsubscribe |
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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

Want to Help the FDA? Become a Consumer Representative on an FDA Advisory Committee
Posted on October 22, 2015 by FDA Voice

The Small Biz Buzz
The Information Source for Regulated Domestic and International Small Pharmaceutical Business and Industry

Commissioner's Fellowship Program

Requesting Speakers from CDRH
U.S. Food and Drug Administration
Protecting and Promoting Your Health
EXTERNAL SOURCES: Newsfeeds, Blogs, Organizations

- **Drug, Device News**: Development & Regulatory
  - FirstWord, MedGadget, MobiHealth News, RF Today


- **Societies, Trade Organizations, Conferences**:
  - Reg. Affairs Professional Society (RAPS)
  - Drug Information Association (DIA)
  - Trade Organization: PhRMA, AdvaMed, MDMA
CONTACT:
elora.gupta1@gmail.com
info@drugdeviceadvisory.com