U.S. Food and Drug Administration
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Managing Risk and Uncertainty Through the Drug Life cycle

Recent FDA Initiatives

Theresa Mullin, PhD

Director
Office of Strategic Programs
US FDA Center for Drug Evaluation and Research

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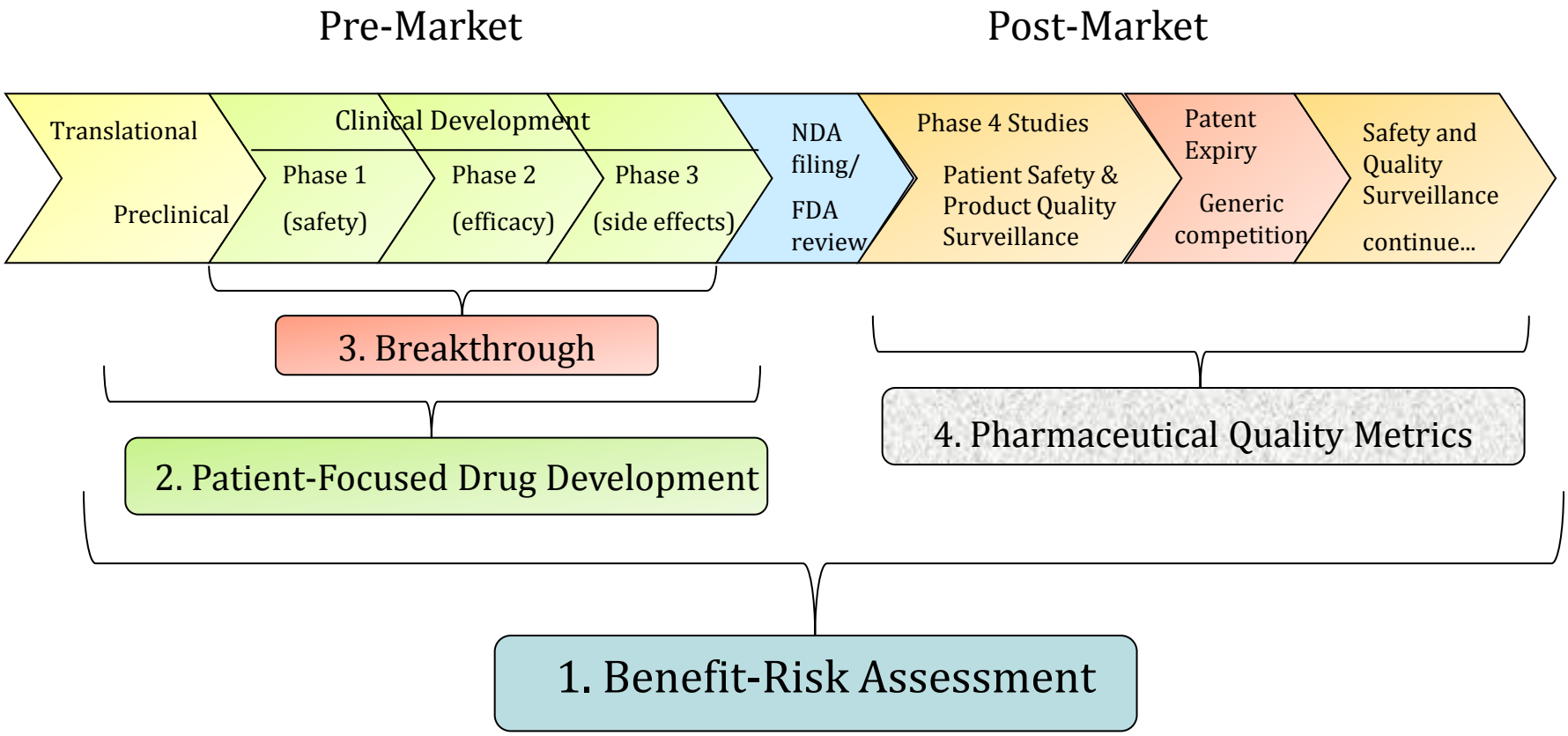
Initiatives in Context of Drug "Life Cycle"



Why Have a Formalized Benefit-Risk Framework?

- FDA makes regulatory decisions based on law and regulations
  - Decisions may be challenged in court and litigated
- Legal standard (for us): decisions cannot be "arbitrary and capricious", i.e., they must reflect a consistent policy, otherwise they are not fair
- Our decisions are our "case law"
  - Each decision is made either in the context of established policy or establishes new policy
- Often remaining uncertainties are HUGE: judgment and values come into play

FDA's Formalized Benefit-Risk Assessment

- Qualitative approach that is grounded in quantification of various data elements. Made at the population level at time of marketing approval:
  - Benefits – Efficacy endpoints from controlled clinical trials
  - Risks – Harms reported in clinical trials and other sources (e.g., spontaneous adverse event reports)
- Evaluation of B-R is dynamic
  - Knowledge of benefits and risks evolves over product life-cycle
- Decisions on B-R require judgment on the part of the regulator and are influenced by:
  - Statutory/regulatory standards
  - Societal expectations
  - Personal values and perspectives

FDA's Benefit-Risk Framework (Columns)

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	For each decision factor… **What is the key information/data that supports your conclusions:** • What you know (facts) • What you don't know (uncertainties and underlying assumptions)	For each decision factor… **What are your overall conclusions about:** • The strength of the evidence • The clinical relevance and significance of the evidence • Any implications on the regulatory decision
Current Treatment Options		
Benefit		
Risk		
Risk Management		
Benefit-Risk Summary and Assessment		

FDA's Benefit-Risk Framework (Rows)

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	**Sets the context for the weighing of benefits and risks:** • How serious is this indicated condition, and why? • How well is the patient population's medical need being met by currently available therapies?	
Current Treatment Options		
Benefit	**Characterize and assess the evidence of benefit:** • How compelling is the expected benefit in the post-market setting? • How clinically meaningful is the benefit, and for whom?	
Risk	**Characterize and assess the safety concerns:** • How serious are the safety signals identified in the submitted data? • What potential risks could emerge in the post-market setting?	
Risk Management	**Assess what risk management (e.g., labeling, REMS) may be necessary to address the identified safety concerns**	
Benefit-Risk Summary and Assessment		

Patient-Focused Drug Development (PFDD)

- Establishing the therapeutic context is an important aspect of B-R assessment
  - Patients are uniquely positioned to inform understanding of this context
  - Current mechanisms for obtaining patient input are often limited to discussions related to specific applications under review

- PFDD offers a more systematic way of gathering patient perspective on their condition and treatment options
  - FDA will convene at least 20 meetings on specific disease areas over the next five years
  - Meetings can help advance a systematic approach to gathering input

PFDD meetings for FY13-15*

FY 2013 (Conducted)

- Chronic fatigue syndrome/myalgic encephalomyelitis
- HIV
- Lung cancer
- Narcolepsy

FY 2014 (Conducted)

- Sickle cell disease
- Fibromyalgia
- Pulmonary arterial hypertension
- Inborn errors of metabolism
- Hemophilia A, B, and other heritable bleeding disorders
- Idiopathic pulmonary fibrosis

FY 2014 – 2015 (to be announced)

- Alpha-1 antitrypsin deficiency
- Breast cancer
- Chronic Chagas disease
- Female sexual dysfunction
- Functional gastrointestinal disorders
- Parkinson's disease and Huntington's disease

*FDA will initiate another process to determine the disease areas for FY2016-17.

Breakthrough Therapy Designation

- The FDA Safety and Innovation Act (FDASIA) Section 902 provides for a new " Breakthrough Therapy Designation"

- A breakthrough therapy is a drug which:
  - Intended alone or in combination with one or more other drugs to treat a serious or life threatening disease or condition and
  - Preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development.

- If a drug is designated as breakthrough therapy, FDA will expedite the development and review of the drug

Breakthrough (BT) vs. Fast Track (FT) Designations

- BT and FT designation programs are both are intended to expedite the development and review of drugs for serious or life-threatening conditions.
  - BT program- preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies.
  - FT program - nonclinical or clinical data demonstrate the potential to address unmet medical need

- BT products obtain rolling review without separately requesting FT designation*

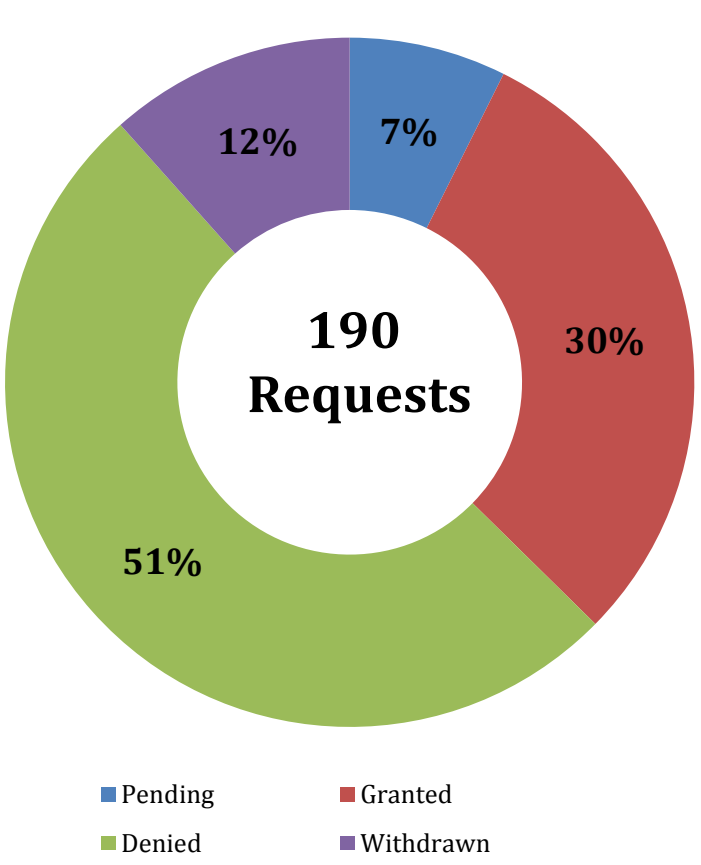
** Expedited Programs for Serious Conditions-Drugs and Biologics*
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

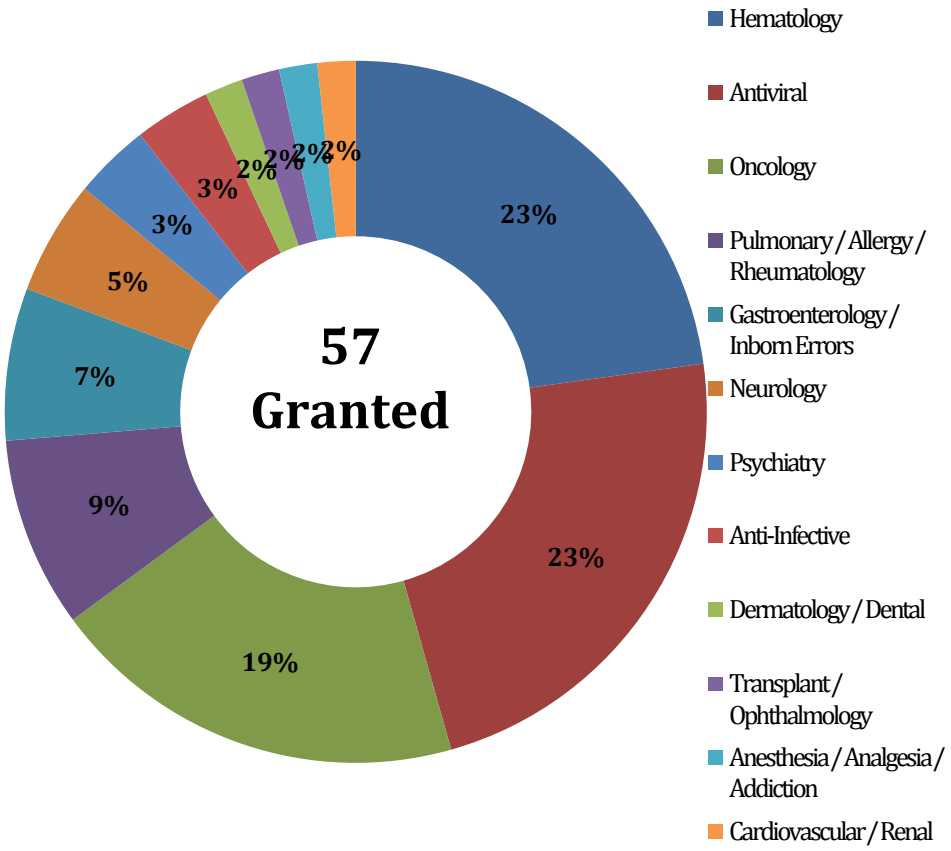
BT Designation Requests

- Submitted when IND first submitted or any time thereafter
- Must have preliminary clinical evidence
- Before initiation of the clinical trial(s) intended to serve as primary basis for demonstration of efficacy to get most benefits of designation
- Rarely after the submission of an original BLA/NDA/supplement

- FDA makes the BT Designation determination –grant or deny—within 60 days

CDER Has Granted 57 Breakthrough Therapy Designations Since Inception*





* Data as of September 30, 2014

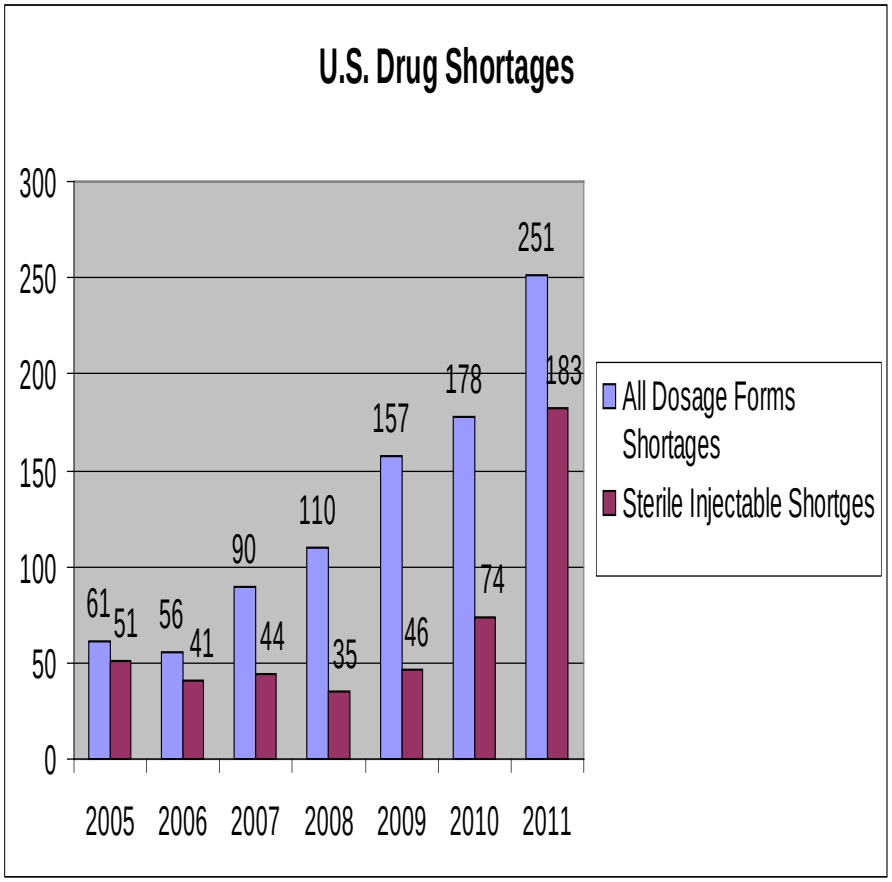
Pharmaceutical Quality Metrics

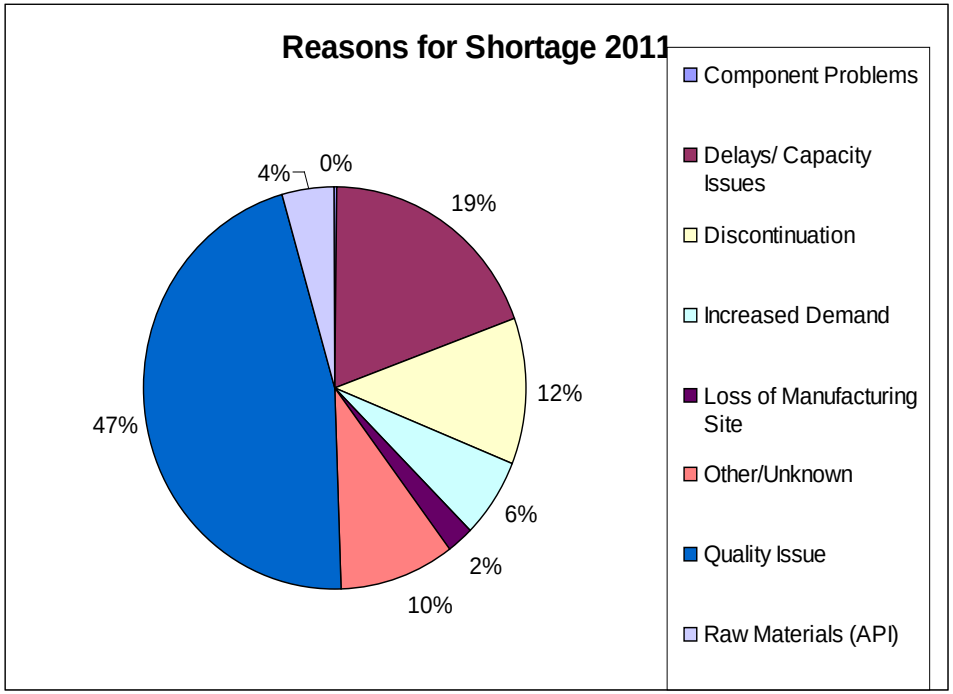
Our vision for Pharmaceutical Manufacturing in the 21st Century:

> *A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight.*

Our observation: We're not there yet

Drug Shortages Continue; Many Involve Quality Problems





Fundamental Problem:

"Inability of the market to observe and reward quality" *

*J. Woodcock and M. Wosinska, Economic and Technological Drivers of Generic Sterile Injectable Drug Shortages, *Clinical Pharmacology and Therapeutics*, 23 January 2013

What are Quality Metrics?

- An objective measure of the quality of a product or process
  - Quality is the fitness for intended use of the product, relevant to patients
  - Product (and/or process) segmentation

- An objective measure of the quality of a site
  - Quality is measure of site's ability to manufacture products fit for intended use
  - Site segmentation (can include a build of product/process scores)

- An objective measure of the effectiveness of systems associated with the manufacture of pharmaceutical products, including the pharmaceutical quality system
  - On site evaluation of quality systems

Metrics Can Raise the Visibility and Reward Quality

- Risk based inspection schedule
- Less frequent inspection for better performing sites
- Potentially predict drug shortages
- Objective evaluation of systems on inspection
- Lower reporting categories for post-market changes

Quality Metrics can help achieve 21st Century Vision for Quality

- For firms, the use of quality metrics promotes responsible practices and quality driven corporate culture
- For public, a focus on quality leads to fewer recalls and quality related shortages
- For FDA, industry achieves and is rewarded for quality, without extensive regulatory oversight

Thank you