Driving Biomedical Innovation by Advancing Regulatory Science



Director

Critical Path and Regulatory Science Initiatives Office of Regulatory Science and Innovation Office of the Chief Scientist/Commissioner

FDA

Issues and Trends in Regulatory Science, 2016







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Disclaimer

This presentation reflects the views of the authors and should not be construed to represent FDA's views or policies.

Innovation is Linked to Ecosystem and Partnerships

FDA-regulated products account for <u>25 cents</u> of every consumer dollar spent in the U.S.

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Impetus for Reform

- "Public and Congress... increasingly disillusioned with the pharmaceutical industry"
- "Several new drugs... found to cause adverse reactions"
- Industry's advertising practices, its high profits, and the high cost of prescription drugs ... under fire"
- Physicians …"joined in criticizing drug advertising as excessive, misleading and…inaccurate" "frustrated by the hard selling pharmaceutical sales representatives"
- "Health care costs ...a subject of scrutiny in Congress and the press"





Regulatory Decision-Making Framework

- FDA decisions are its "case law"
- Each decision is made either in the context of established policy (i.e., allowable impurity level) or establishes new policy
- Science, which is a system for established, agreed-upon experimentally-based facts, cannot make decisions



Role of Judgment and Values in Regulation

- Judgment: how does this decision comport with established policies and legal interpretation?
 - Big picture impact
 - Effect on other decisions
- Values: what each stakeholder/individual weighs most strongly (wide differences here !)
- The more uncertainty, the greater the play of judgment and values





Need for Decision Analysis

- FDA cannot make ad hoc or one-off decisions based on how we feel about a particular matter
- Decisions must be fair and thus consistent, not arbitrary and capricious; they must be within a policy framework
- One of the triumphs of FDA medical product regulation is its contribution to evidence-based medicine



Overview

• FDA basics to regulate products

- Legal authorities; Regulatory triggers: Product vs Process
- FDA Centers, separated and united by responsibilities
- Challenges and opportunities of regulatory processes for different products
 - Implications of FDA's regulatory approaches
- Building preparedness by advancing regulatory science
 - Office of Chief Scientist and ORSI
 - Critical path initiatives and regulatory science
 - Programs to support better science, better training and better networking



• Food /Drug Laws typically passed on heels of tragedy

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- Horse named Jim started it all: fatal transmission of tetanus through antitoxin – 1902 Biologics Control Act
- Food scandals of ~1900 (e.g. borax), Harvey Wiley and the "Poison Squad" 1906 Pure Food and Drug Act – created food/drug regulation – allow action on safety
- Sulfanilamide with antifreeze killing over 100, DNP and blindness: 1938 FD and C Act – allowed premarket safety review and an action not to approve but did not require approval
- Thalidomide (tragedy averted) and Kefauver-Harris Amendments: pre-market safety and efficacy review and approval (1962)
- Melamine, heparin, compounding....next?
- Sound regulation critical to protect the public and assure confidence in industry and public health
- There also are health care and human costs of ineffective or marginally effective products (which can also displace use/study of more effective therapy) – thus the lack of efficacy is also a safety issue



What does FDA do?

- Mission: Protect and promote public health
- Protect:
 - Assure safety, effectiveness and security of human and veterinary drugs, vaccines, other biological products, medical devices, food, cosmetics, radiation-emitting devices
- Promote:
 - Help speed innovations that make needed products available, and where possible, more effective, safer and affordable
 - Provide accurate, science based information to maximize product benefits and reduce risks
 - Enhance preparedness by facilitating the development and availability of Public Health Emergency Medical Countermeasures
- Regulate tobacco products

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What does FDA not do?

 Regulate medical/veterinary practice, services, or pricing

What does FDA not regulate?

 Alcohol, consumer products (unless radiation emitting), illicit drugs, health insurance, meat and poultry (except drug residues), pesticides, restaurants, grocery stores, water, advertising (excluding for drugs and medical devices), reproduction/breeding



FDA's Legal Authorities

- Statutory Authorities (law), for example,
 - Food, Drug and Cosmetic Act
 - Public Health Service Act
 - FDAAA, FDASIA, -UFAs, etc.
 - National Environmental Policy Act
- Regulations (outline), for example, Code of Federal Regulation, Title 21
 - GMPs, section 211
 - INDs, section 312
 - Biologics, sections 600, 610, etc
- Guidance Documents (best practice, iterative)



FDA Faces Many Challenges

- Rapid scientific breakthroughs and emerging technologies resulting in novel products that may raise unique testing and safety issues
- New and evolving public health threats
- Globalization of public health, science, manufacturing and supply chains
- Providing accurate and useful consumer information in age of information overload from multiple sources

Globalization Challenges

•Globalization has led to dramatic increases in imports and to highly complex supply chains creating increased opportunities for counterfeit and adulterated products to reach consumers.

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•Science and policy solutions needed





Supply Chain for Canned Tuna





Some Globalization Statistics

FDA-regulated products originate from more than:

- 150 countries
- 130,000 importers
- 300,000 foreign facilities
- >35 million import lines in 2015
- Overall number of FDA-regulated shipments at over 300 U.S. ports has quadrupled over ten years
 - 28 million shipments
- Distinction between domestic and imported products is largely obsole

A high end estimate anticipates a tripling of imports of FDA-regulated products between 2007 and 2015

And More Globalization Statistics

Food

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- 10-15% of all food consumed by U.S. households is imported
- ~ 50% of fresh fruits and 20% of fresh vegetables imported
- 80% of seafood eaten domestically is from outside the U.S.
- Food imports increased 10% per year from 2005 on

Devices

- At least 50% of all medical devices used in the U.S. are imported
- Medical device imports grew at over 10% per year from 2005 on

Drugs

- At least 40% of drugs on U.S. shelves come from overseas
- 80% of API manufacturers are located outside the U.S.



Supply Chain Tragedies

msnbc

Tainted cough syrup kills 21 in Panama

CDC investigation traces mysterious deaths to industrial chemical

Ap Associated Press updated 5:51 p.m. PT, Fri., Oct. 13, 2006

Ehe New Hork Eimes

November 26, 2008

WORLD BRIEFING | AFRICA

Nigeria: Contaminated Medicine Blamed for Deaths

Most popular

June

Ehe New York Eimes

May 7, 2007 80 children die in Haiti due to contaminated glycerin in acetaminophen syrup

The New York Times

Heparin Contamination May Have Been Deliberate, F.D.A. Says



INTERNATIONAL HE GLOBAL EDITION OF THE NEW YORK TIMES ASIA & Pacific

China recalls infant formula

By Keith Bradsher

Published: September 12, 2008

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FDA's Actions

Working to strengthen the global product safety net...





FDA Foreign Posts





Multilateral and Bilateral Relationships

- Over 30 arrangements with foreign counterparts
- Joint inspections
- Harmonization and standard-setting efforts
- Training with counterpart agencies to increase understanding of FDA regulations
- Regulatory capacity building

From Globalization Challenges and Policy to Regulatory Science Solutions

FDA developed **Counterfeit Detection Device** (CD3), a low-cost, convenient, effective tool detect counterfeit or adulterated products.

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Uses variety of light wavelengths, from UV to IR, to screen for changes in products/packaging
Real-time, portable, does not require technological expertise

•Intercepts suspect shipments/products for further testing, allowing more effective screening and use of resources

•Reduces risks from counterfeit products



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~1906

2014



A name is not a regulatory trigger

GMO....genetically engineered.....transgenic.....gene/genome edited/ing.....techniques of modern biotechnology.....SynBio....

...are NOT regulatory triggers for the Federal Food, Drug and Cosmetic Act.



So What is the Regulatory Trigger?

The term "drug" (for example) means

- (A) articles recognized in the official United States
 Pharmacopoeia, official Homoeopathic Pharmacopoeia
 of the United States, or official National Formulary, or
 any supplement to any of them; and
- (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and
- (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and
- (D) articles intended for use as a component of any article specified in clause (A), (B), or (C).



Challenges: Product vs Process

• FDA regulates "articles" or products; not the processes by which they are made.

BUT

• Manufacturing processes may affect safety, effectiveness, purity, potency, etc.



FDA administrative structure



27



Medical Product Lifecycle Overview





Drug and Biologic Product Life Cycle







Redefine patient as co-inventor

- 1. Drive science
- 2. Drive smart product development
 - 1. Digital engagement- app, web, social media
 - 2. Data driven
 - 3. Patient information- digital media
 - 4. Continuity of care, compliance

Better performance and outcome

Stratify patients by:

- Genetics
- PRO's
- Behavior
- Disease definition



- New product review and pre-market approval
 - Proactive interactions during review process
 - Written reviews (pre-clinical, clinical, manufacturing data, facilities) and decisions
- Monitoring
 - Manufacturing quality and safety
 - Safe handling

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- Adverse events/new risks/populations
- Communication to patients and providers
- Enforcement/Compliance
- Research targeted to safety, efficacy, quality



What occurs Pre-approval?

- FDA reviews application and data to determine if product benefits outweigh risks
 - Evaluates whether studies (and data) submitted are adequate and well controlled and show that the product is safe and effective for proposed use (indication) and populations
 - Determines whether FDA agrees with sponsor's conclusions and/or whether additional information is needed
 - For generics (ANDA) data required focused on drug quality and bioequivalence vs. clinical efficacy studies needed for NDA
 - For some devices, use of the 510k pathway may allow approval based on substantial similarity to previously cleared device, clinical data may not be required
 - For novel products, an advisory committee is typically convened to consider data, including presentations by both FDA and the sponsor, and vote on questions including efficacy and safety for intended use – FDA is not bound by AC recommendations



Approaches to Speed Product Review, Access and Approval to Meet Unmet Medical Needs for Serious Conditions

- Fast Track designation (allows rolling submissions)
- Priority Review (6 vs. 10 month cycle)
- Accelerated approval can use likely surrogate endpoints followed by confirmatory study
- Breakthrough designation: if promising initial data
- Availability under special access programs
 - eIND, treatment IND, HDE
 - For emergency medical countermeasures during public health emergency, EUA (now pre-EUA possible)



Standards of Licensure Drugs and Biologics

- Safety
- Purity
- Potency
- Stability
- cGMP Compliance



What Occurs Post Approval?

- Rare adverse events (AEs), uncommon or unpredicted drug interactions and/or efficacy issues in special populations, may not be apparent pre-approval based on 100's-1000's of RCT subjects
- Post-marketing studies (Phase IV) may be required and/or performed to address special populations, safety concerns/signals
- Review of AEs "passively" reported to FDA (e.g. through MedWatch, VAERS). Caveats: underreporting, complexity of determining etiology in clinical setting, lack of ideal control data/denominators
- Increased use of active monitoring for specific AEs (e.g. health care based or CMS based data, PRISM, Sentinel).
- Findings of concern made public and may be brought to Advisory Committees and/or result in labeling change, warning or withdrawal
- Manufacturing quality oversight and inspections also continue
- Shortage monitoring and remediation activities, counterfeit detection
- Monitoring of promotional activities



Some Examples

- Bioterrorism, pandemics, emerging infections
- New food pathogens
- Complex, global supply chains for foods, drugs, source materials and ingredients
- Antibimicrobial Resistance
- Emerging chemical concerns such as "endocrine disruptors", trace contaminants

• Counterfeit and sub-potent drugs

- Gene and cell therapies
- Personalized medicine (and related diagnostics)
- "Big data"
- Novel materials: nanotech, tissue engineering, 3D printing etc., human-machine interfaces
- Engineered foods, from organisms or *in vitro* food
- Synthetic Biology

Path Forward: Dialogue and Preparedness with appropriate resources

- The best way to understand the likely regulatory path(s) a product may have to navigate is to talk with FDA early about the product and its intended use(s).
- Early interaction also aids in

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- identifying safety and other regulatory issues early in the development process, and
- making the regulatory process more predictable.
- Advancing Regulatory Science and Coordinated Framework(s) are essential in addressing challenges from emerging science, technologies and novel products

Why Do We Need Regulatory Science ? Attrition Rate too High, Process too Expensive





Why Regulatory Science?

- Major investments and advances in basic science are not effectively translating into products to benefit patients
- Product development is increasingly costly, success rates remain low. Failures often related to predictive science used in evaluating efficacy and/or safety
- For new technologies, manufacturing science also a problem
- Development/evaluation tools/approaches have neither kept pace with nor incorporated emerging technologies
- And....it's about our nation's health and our economic well being, the *health* of the 25% of the economy fueled by the research and innovation that FDA regulates
- FDA's essential role recognized in the President's *National Bioeconomy Blueprint*, including forging public-private partnerships to improve health outcomes and reduce costs.



Regulatory Science Overview (cont.)

- FDA scientists see what works and what doesn't across multiple products – and can help innovators avoid pitfalls and failure
- Strong tools and expertise at FDA reduce risks of two kinds of errors
 - Worrying about signals or issues that can be understood to not represent risk
 - Missing true risk
- Particularly important for new/emerging technologies where experience and standards are lacking, and uncertainties, including about safety, common
- Unlike work typically supported by NIH and performed in academia or by individual sponsors or companies (often single product-oriented) and becomes available to all



What is Regulatory Science?

 The science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of products

Science, always with some uncertainty, is the basis for virtually every FDA regulatory action or decision



Regulatory Science Defined

- The application of science to the development and utilization of new tools, standards, and approaches for the assessment of medical product efficacy, safety, and quality
- A critical bridge between basic scientific research discoveries and new marketed, medical products.
- Evidence-based science should be the foundation upon which regulations are based and put into practice.



FDA Strategic Plan for Regulatory Science



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- Identify opportunity areas of regulatory science essential to the success of FDA's public health mission
- Develop/use the 21st century regulatory science tools and approaches for evaluation of 21st century products
- Promote innovation through targeted and collaborative approaches to regulatory science that enable new technologies and product development
- Build FDA's scientific capacity, infrastructure, culture and collaborations, including through scientific and professional development of FDA's scientists



Strategic Priority Areas

- 1. Transform Toxicology to Enhance Safety
- 2. Stimulate Innovation in Clinical Trials and Precision Medicine
- 3. Support New Approaches to Improve Product Manufacturing and Quality
- 4. Ensure Readiness to Evaluate Innovative and Emerging Technologies
- 5. Harness Diverse Data through Information Sciences to Improve Health Outcomes
- 6. Implement New Prevention-Focused Food Safety System to Protect Public Health
- 7. Facilitate Development of MCMs to Protect U.S. and Global Health and Security
- 8. Strengthen Social and Behavioral Science to Help Consumers and Professionals Make Informed Decisions
- 9. Develop Global Product Safety and Surveillance Network 44



Recent Examples of Regulatory Science Promoting Innovation and Reducing Costs

- In silico modeling of MRI safety to enable new MRI-safe implantable devices
- Faster potency and sterility assays to speed product release, both in an emergency or routinely
- New tools to detect hidden software flaws in complex devices
- Use of pooled FDA data to identify a biomarker as an endpoint for drug development for pediatric pulmonary hypertension
- Use of adult data and modeling to determine, where appropriate, drug efficacy in pediatrics, avoiding unneeded clinical trials
- Rapid development of assays to assure safety of Gulf seafood and allow reopening when safe
- New molecular tests, including HTS, to trace sources of foodborne outbreaks more quickly AND accurately



FDA administrative structure



46



Advancing Regulatory Science at FDA

FOOD AND DRUG ADMINISTRATION





Commissioner's Office: Key Activities

- Develop and articulate FDA's overarching strategic direction, manage external (Office of External Affairs) and legislative (Office of Legislation) relationships/outreach. Represent FDA to other agencies, departments
- Manage "directorates" as coordinating entities for medical products, foods, operations, and global operations/inspectional/international activities
- Support key cross-cutting infrastructure (e.g. facilities, HR, IT – Operations Directorate) and activities (e.g. Office of Special Medical Programs for combination & orphan products, pediatrics, advisory committees)
- Foster coordination, consistency, efficiency across program areas in policy (Office of Policy), law (Office of Chief Counsel) and science (Office of the Chief Scientist)
- Address issues and disputes that rise above Center level



Example: Advisory Committee Oversight and Management Staff

- Protect and enhance quality and integrity of regulatory decision-making
- Obtain outside, independent, and diverse expert advice and recommendations
- Allow for open, public discussion of important issues
- 33 FDA ACs, 18 Device Panels, ~ 85 meetings/year
- ~620 members, diverse academia, clinicians, industry, patients and consumers
- Opportunity for public input at AC meetings



Types of Topics Brought To ACs

- Product approvals
- Major adverse event reporting/labeling issues
- Product manufacturing/quality issues
- Risk Communication and Management
- Review of major agency initiatives and programs, cross cutting scientific matters

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Some Other Ways FDA Gets Input

- Formal: Public comment opportunities on proposed rules (posted in Federal Register), which are FDA's primary regulatory requirements to ensure compliance with food and drug laws, and ultimately have legal enforceability.
- Public comment opportunities on draft FDA guidances (which provides FDA's guidance on how to comply with regulations)
- Individual advisors/consultants (SGE's)
- Informal: scientific meetings, workshops (often cosponsored with others) FDA participation at and/or liaison to other meetings/organizations



Power of PPP's: Examples of FDA Engagement

- Biomarkers Consortium engages FDA, NIH, industry, patients
 - I-SPY 2 trial incorporating multiple companies and academics in evaluation of 5 new agents in a novel study design for breast cancer
- ADNI: Alzheimer imaging & biomarkers
 - With NIH, 13 companies, 1300+ patients
 - Standardizing imaging methods, identifying predictive host genetic and CSF biomarkers
- Coalition Against Major Diseases
 - With patient groups, ~ 15 companies
 - Focusing on clinical data standards and early identification of neurodegenerative diseases
- OMOP: with academia, pharmaceuticals, health data systems
- CERSIs: academic research and training partnerships



Critical Path and Regulatory Science Initiatives

- More than 60 Regulatory Science-Critical Path Initiative projects (with CBER, CDER, NCTR, CVM, CDRH, CFSAN)
- FDA collaborates with more than 30 organizations on RS-CPI projects
- Research programs and science support areas
 - FDA intramural research grants
 - FDA wide science and research core infrastructure support
 - FDA wide SME scientific working groups
 - CERSI Centers of Excellence in Regulatory Science and Innovation
 - Technology Transfer and Strategic Partnerships
 - BAA Broad Agency Announcement to advance regulatory science
 - Communication, information and training hub (collaboration with OSPD, including the FDA Clinical Investigator Training course)



Prioritization

at Center level: Regulatory Science Subcommittees (Critical Path Steering Committees)

- Vetting via internal advisory boards made up of staff from all the Center offices and all levels
- Identify scientific needs and balance with emerging needs to establish priorities for the Centers

FDA-wide:

Scientific SME Working Groups and Councils CERSI Steering Committee Senior Science Council Executive Leadership Council



CERSI Overall Goals

- Strengthen the science needed to transform product development and evaluation by leveraging cutting-edge collaborative research.
- Scientific exchange, and training for FDA, Academia, and all other stakeholders; nationally and internationally.
- Collaborative research in the priority areas of regulatory and translational science.

CERSIs serve as communication and action platforms for all stakeholders "across the isles":

- Dialogue and culture change strategic alliance beyond single projects
- Research prioritization/direction

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- Problem solution on specific issues and/or broad basis
- Conflict mitigation, harmonization and (consensus) standardization
- Information, education, training; FDA workforce and national professional development



CERSI Workshops

Workshop Topic	CERSI	Event Date/Location
Building the National Evaluation System for Medical Devices: Using Real-World Evidence to Improve Device Safety and Effectiveness	UM CERSI	March 24, 2016 UMD School of Pharmacy 20 N. Pine Street, Rm. N103
Quantitative Assessment of Assumptions to Support Extrapolation of Efficacy in Pediatrics	UM CERSI	June 1, 2016 FDA White Oak
Pediatric Master Protocols	UM CERSI	Sept. 23, 2016 FDA White Oak
Substitutability of Generic Drugs: Perceptions and Reality	JHU CERSI	November 18, 2016 FDA White Oak
Patient Preference Study Methods	All CERSIs	April 2017 FDA White Oak
Natural Language Processing: Potential to Improve the Quality and Completeness of Data Used in Pharmacoepidemiologic Electronic Health Record Studies	UCSF- Stanford CERSI	June 2017 FDA White Oak

Opportunity is in Complexity

- Successful drug (product) regulation requires that FDA perform at a high level in
 - Science

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- Law
- Medicine
- Policy
- Management and execution
- Political and stakeholder engagement



Partnerships and Collaboration

- Today's challenges are too complex for any one party or sector to solve
- Urgent public health situations have *required* robust publicprivate partnering, formal or informal, for timely success
- Such challenges provide models for innovative partnering, and for culture change, both inside and outside government
- FDA is actively engaged and welcomes more ideas/models





Summary

- Modern food and drug law, which keeps us safe, has arisen primarily in response to tragedies
- FDA's product specific review and surveillance occurs primarily through its product Centers and continues throughout the product lifecycle
- The Office of the Commissioner provides crosscutting coordination, strategic leadership and support, with the Office of the Chief Scientist serving as an advocate and enabler for scientists and the scientific enterprise, and public health preparedness, at FDA.
- Globalization and emerging technologies provide both opportunities and challenges
- Regulatory science is critical to provide tools needed to enhance our biomedical enterprise, economy, speeding products to patients, safely, addressing new technologies and challenges.
- The work is too complex for one party or sector.
- New collaborative models, both inside and outside government, are essential for success.





New Paradigm for Product Development





Advancing Regulatory Science for Public Health



THANK YOU