

The Public Health Role of Drug Regulation in the US

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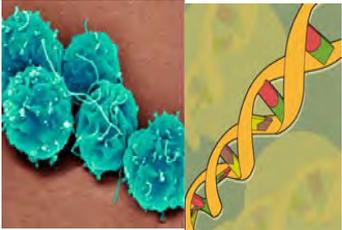
Disclosure Statement

I have no financial relationships with proprietary entities that produce health care goods and services

The opinions and information in this presentation are my own and do not necessarily reflect the views and policies of the FDA



FDA's Regulatory Scope: 20 cents of every GDP dollar





FDA Mission

FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.



FDA Mission

FDA is also responsible for advancing the public health by helping to speed innovations that make medicines more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medicines and foods to maintain and improve their health. FDA also has responsibility for regulating the manufacturing, marketing and distribution of tobacco products to protect the public health and to reduce tobacco use by minors.



FDA Mission

Finally, FDA plays a significant role in the Nation's counterterrorism capability. FDA fulfills this responsibility by ensuring the security of the food supply and by fostering development of medical products to respond to deliberate and naturally emerging public health threats.



A Brief History of FDA Regulation and Its Impact on Good Science

- 1890s – Discovery of diphtheria antitoxin gave rise to increased production
- 1901 -- Problems from both public and commercial labs, especially tetanus deaths from contaminated diphtheria antitoxin and smallpox vaccine
- 1902 – Passage of Biologics Control Act



A Horse Named Jim



1902 Biologics Control Act

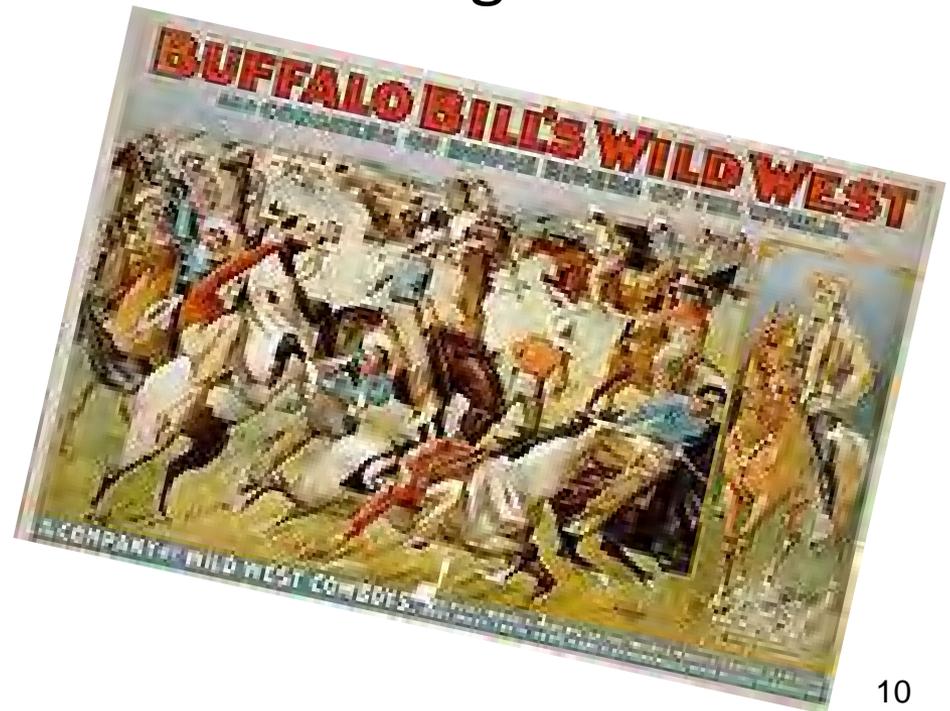
- Scientifically trained staff must supervise production of these medicines
- Licensing of facilities by PHS
- Inspections of establishments and testing of biologics for purity and potency
- Standards issued for products
- Enhanced scientific legitimacy on firms and their products
- Scientific infrastructure mandated under the law helped promote new product development.

Pre-1938

FDA could only respond to problems when identified

- No requirements for testing or approval
- No data of any kind had to be submitted before marketing
- Government could seek to remove dangerous or misbranded products.

Not surprisingly, there were some disasters:



Notable Disasters Before 1938

- Dinitrophenol – weight loss drug, caused thousands of cataracts, enucleations in the 1930's.
- Elixir sulfanilamide – sulfa drug killed over 100 people in 1937, many of them children; diethylene glycol (anti-freeze) was the solvent. No animal testing. A chemist simply smelled and tasted the elixir.



These events led to →



The Food, Drug and Cosmetic Act of 1938 (FD&C) – Age of Safety

Two Requirements:

1. Pre-market notification
2. Demonstration of safety

Next Major Turning Point: Thalidomide

1,200 U. S. DOCTORS GOT BANNED PILL FOR TESTS

Thalidomide, the sleeping pill that has caused thousands of infant malformations in Europe had been distributed to 1,200 physicians in the United States for investigational use since 1959, before it was banned in the United States.

This figure has been supplied by the William S. Merrell Co. of Cincinnati, manufacturer of the drug, to the Food and Drug Administration here. FDA inspectors are now checking the physicians to make sure they have returned or destroyed their supplies of the drug, as requested by the Merrell Company in March.

The investigational use of the drug in the United States dates to 1959. It is not known by FDA if the drug was used experimentally during early pregnancy, the critical period in which the malformations are caused.

Several malformed infants in the United States have been linked to their mothers' use of the drug. In none of these publicly-reported cases, however, was the drug given by a licensed physician in the United States.

The Age of Effectiveness:



The 1962 Kefauver-Harris Amendments

Not obvious why thalidomide (a safety problem) led to a requirement for demonstrating effectiveness, but the 1962 Act made at least 3 important changes:

1. FDA had to give positive approval before a drug could be marketed
2. A meaningful requirement to study drugs under an IND and an explicit requirement for informed consent (one year before the Declaration of Helsinki).
3. The effectiveness requirement



Dr. Francis Kelsey received the President's Award for Distinguished Federal Civilian Service



Since 1962: The Era of the RCT and the Value of Empiric Testing

- Growth of the medical product development enterprise
 - Non-clinical models of disease
 - Statistics of trials assessment
 - Placebo- and Active-controls
 - Clinical efficacy and safety assessment
- Sobering experiences where predicted impact of new therapies was badly wrong:
 - Autologous bone marrow transplantation for treating breast cancer
 - Suppression of PVCs with anti-arrhythmics
 - Health effects of chronic non-steroidal use



Context:

New Realities in the 21st Century

- Previously we lacked effective treatments for most life-threatening illnesses
- Today many more treatments are available, but patterns of manufacturing, public scrutiny of healthcare, and information available to guide use have shifted dramatically. Patients and clinicians need:
 - New products sooner
 - Accurate, up-to-date and understandable information
- Result: increased public and Congressional scrutiny of CDER's decisions

FDA's Challenges for the 21st Century



- Supporting Innovation and Advances in Science and Technology
 - Better understanding of the mechanisms of disease and human biology
 - Advances in biomedical engineering
 - Increasingly complex products; challenges for development, as well as assessment of safety, efficacy and quality
- New Authorities and responsibilities given us by Congress
 - Food Safety Modernization Act
 - Food and Drug Administration Safety and Innovation Act
 - Drug Quality and Security Act
- Globalization
 - Just as disease knows no borders, product safety and quality no longer know any borders
 - We live in an increasingly complex, global regulatory landscape.



The FDA Today: Embracing Science-Driven Regulation and Innovation

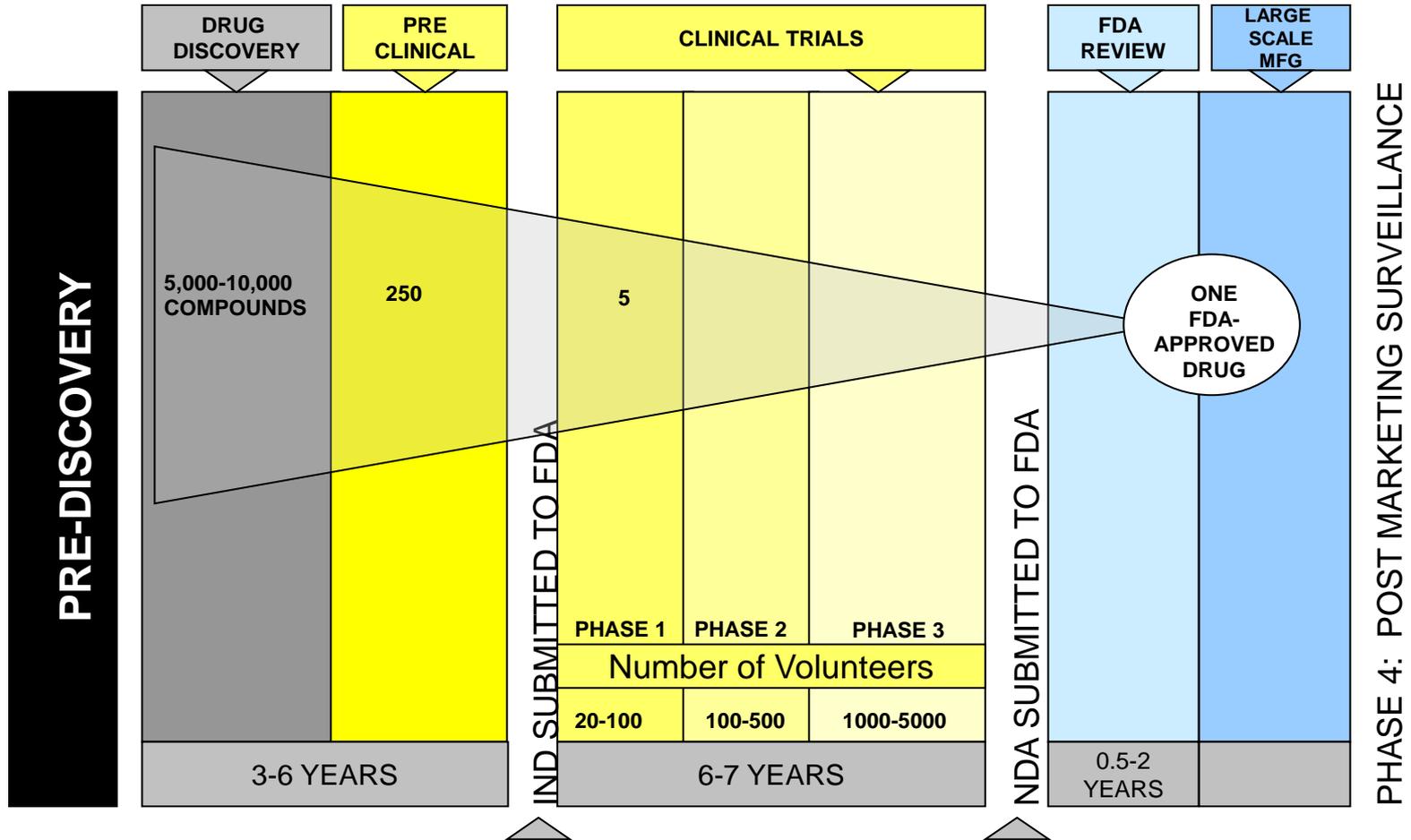
Maintaining the Balance

- The task for FDA's scientist is to strike the right regulatory balance – between providing fast access to new products the one hand, and preventing harm to public health on the other
- When done right, regulation can be a pathway to achieve meaningful and lasting innovation, allowing FDA to deliver on the promise of science in the service of patients, consumers, and industry

Critical Part of FDA Work: Sustaining Medical Product Innovation

- High failure rates for drug development
- Rising R & D costs
- A limited pipeline of potential drugs
- A lack of basic information about the causes of the disease and the pathways for slowing its progress

R & D Process



Improving Evidence Generation Essential





Changes are Needed to Our National Clinical Research System

- High percentage of decisions not supported by evidence*
- Health outcomes and disparities are not improving
- Current system is great **except**:
 - Too slow, too expensive, and not reliable
 - Doesn't answer questions that matter most to patients
 - Unattractive to clinicians & administrators

We are not generating the evidence we need to support the healthcare decisions that patients and their doctors have to make every day.



We Need An Efficient Evidence Generation System....

- More data available than ever in new forms
- Much more of clinical practice could be guided by high quality evidence
- Clinicians and their practice organizations could focus on interpreting the evidence and applying it
- The role of opinion and expertise would be at least as important, but it would be put to a much higher purpose—providing precision healthcare

Many Stakeholders in Clinical Trials Enterprise



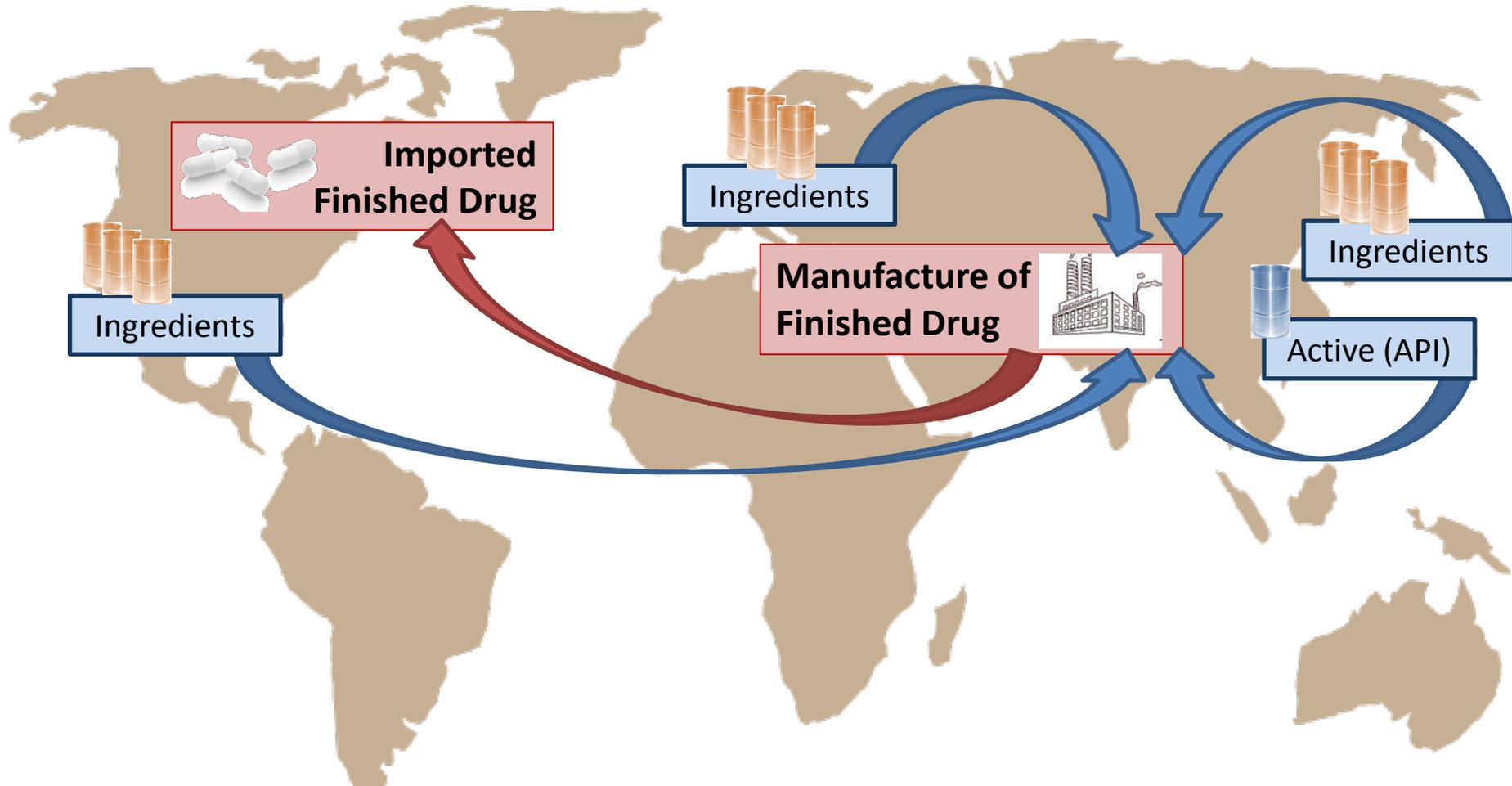


Critical Part of FDA Work: the Challenges of Globalization to Product Quality and Development

- When FDA was established more than a century ago:
 - Our regulated industries were predominantly local
 - The volume of imported produce was low
 - The movement of good across country (and between countries) was minimal



The Global Drug Manufacturing Supply Chain



ingredient (API) made in China and ingredients made in Europe, Japan, or the U.S. These components may shipped to India where the finished drug is manufactured and then imported into the U.S. for distribution.



Old Shenzhen (1982)





New Shenzhen (2013)



Imports Continue to Increase

- **Food**
 - Approximately 49% of fresh fruits and 25% of vegetables are imported
 - 89% of seafood eaten domestically comes from outside the United States
- **Devices**
 - Based on dollar values, at least 35% of all medical devices used in the United States are imported
- **Drugs/Biologics**
 - 80% of Active Pharmaceutical Ingredient manufacturers are located outside the United States
 - Based on dollar values, more than 40% of biologics are imported
 - 40% of finished drugs come from overseas



The Impact of Globalization on FDA's Mission

- **Foreign production of FDA-regulated goods and materials has exploded over the last decade**
- **FDA-regulated products originate from more than:**
 - 150 countries
 - 130,000 importers
 - 300,000 foreign facilities
- **Number of FDA-regulated shipments at 300 U.S. ports has more than doubled during the last ten years.**
 - From 2006, shipments of imported food and medical products crossing our borders went from approximately 15 million to 34 million

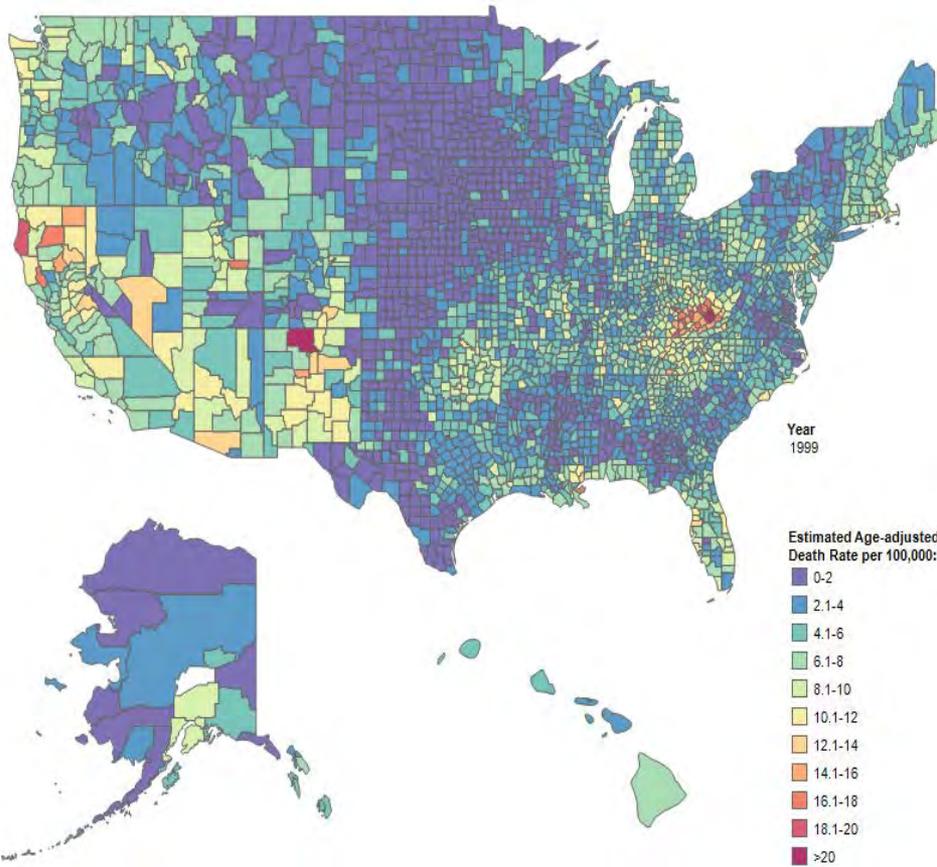


Critical Part of FDA Work: Responding to New Challenges

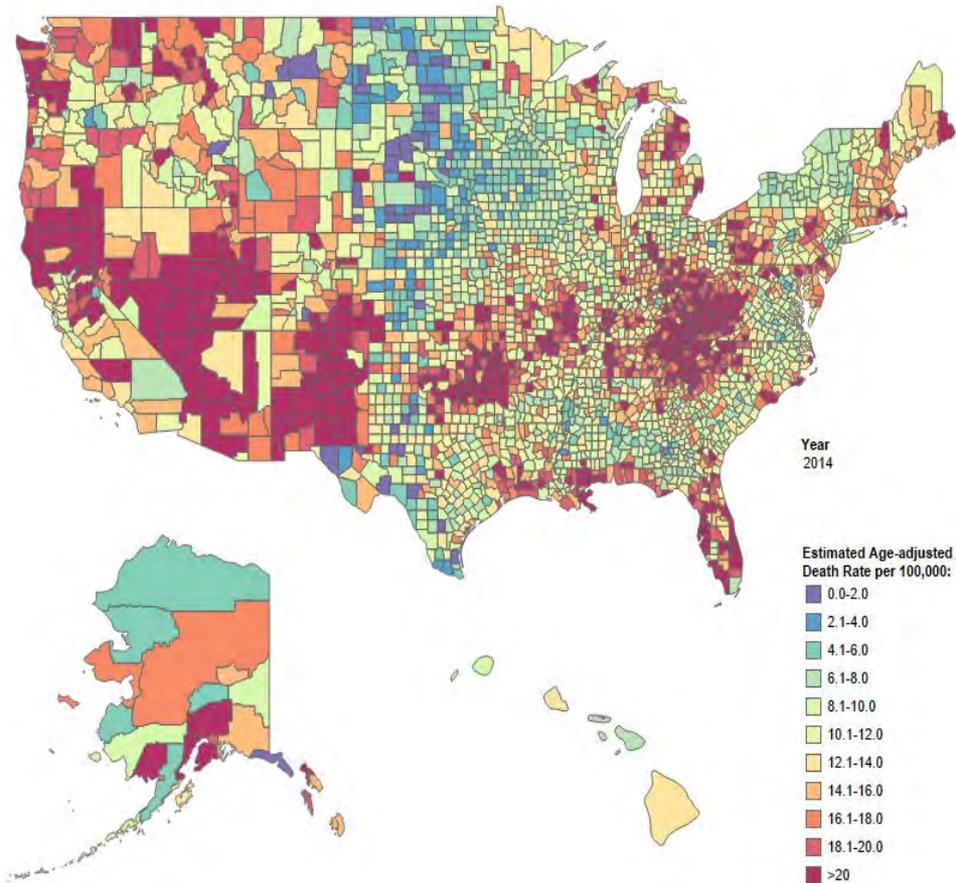
- Public health challenges need to be addressed promptly and fully as they arise
- Part of FDA mission -- ‘Protect and Promote’
- Contaminated compounded steroids and heparin
- Prescription opioid abuse
 - Complex medical, social, scientific issue
 - Over 15,000 overdose deaths in US last year associated with opioid use

Overdose Death Rates

1999



2014



Designed by L. Rossen, B. Bastian & Y. Chong. SOURCE: CDC/NCHS, National Vital Statistics System

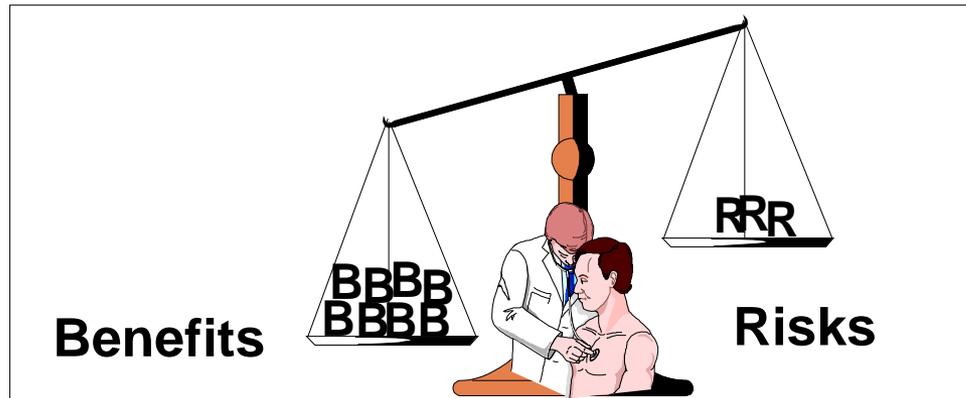
Science = Solutions

Important: FDA One of Many Stakeholders

FDA
evaluates
benefits/risks
for the population



Provider
evaluates
benefits/risks
for a patient



Patient
evaluates
benefits/risks
in terms of
personal values



FDA Organization



Office of the
Commissioner



Office of
Regulatory
Affairs



Center for
Food
Safety &
Applied
Nutrition



Center for
Drug
Evaluation
& Research



Center for
Biologics
Evaluation &
Research



Center for
Devices &
Radiological
Health



Center for
Veterinary
Medicine



National
Center for
Toxicological
Research



Center for
Tobacco



FDA's Current Resources

- Total annual budget \$4.39 billion for FY 2014
- User Fees – \$1.83 billion, approximately 42% of total
- Appropriated Funds – \$2.56 billion, about \$8 per citizen
- 15,705 FTEs, 77% with college degrees, 21% with doctorates
- 223 U.S. offices and 13 laboratories
- 11 international offices and posts in 8 countries

Who Works at FDA?

- Chemists – review the drug substance, product, and manufacturing process
- Biologists – review biological products
- Toxicologists – review the non-clinical studies
- Pharmacologists – review drug pharmacokinetics, exposure-response, drug-drug interactions
- Statisticians – review all types of studies; design and analysis
- Physicians & Pharmacists – review clinical protocols, safety and efficacy data
- Manufacturing science specialists
- Engineers
- Project managers – the glue that holds us all together



FDA's Reliance on Industry User Fees

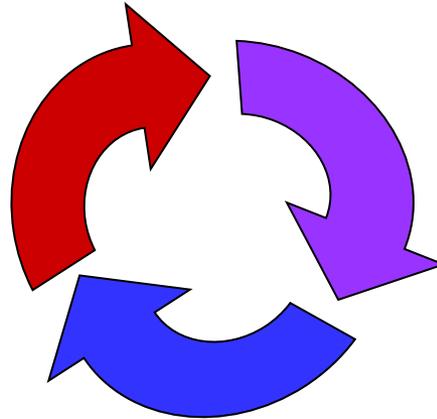
- Approximately 42% of FDA's funding comes from industry user fees: \$1.83 billion
- Industry user fees provide 64% of the funding for FDA's human drugs program, which itself accounts for approximately 30% of FDA's budget
- FDA's medical device program accounts for 10% of FDA's overall budget; user fees fund 25% of that program
- FDA's foods program is 21% of its budget, but just 2% of that program is funded by industry user fees
- FDA's tobacco regulatory program is fully funded by industry user fees

What is the Role of the Regulator in Responding to Public Health Challenges and Supporting Innovation?

FDA: First Focused on Core Business Functions

Pre-Market Review

Assessment of safety and effectiveness of new medical technology & safety of new food ingredients



Product Safety & Compliance

Inspection of manufacturing facilities and products to assure safety, quality & compliance with FDA regulations

Consumer & Patient Safety

Post-marketing surveillance to ensure the safety of consumers & patients who use FDA-regulated products

5 “Moral Imperatives” of Government Regulation



- Protect the Public from Harm
- Preserve Maximum Individual Freedom of Choice
- Guarantee Meaningful Public Participation in the Decision-Making Process
- Promote Consistent and Dependable Rules that are Equally Applicable to Everyone
- Provide Prompt Decisions on All the Issues that Arise in a Regulatory Context



Role for the FDA Beyond These Core Functions to Aid Innovation

- We are uniquely situated to contribute to innovation:
 - Legal role in application of regulations
 - Focus on public health mission
 - Regulators in unique position to see needs across disease areas
 - Regulators in unique position to respond to needs
 - Regulators have identified obligation to support improved regulation, aided by harmonization/convergence



Role for the FDA Beyond These Core Functions to Aid Innovation

- Expanded FDA role
 - c/w mission: ...‘promote’ the availability of novel medical therapies for the US population
- Provide clear roadmap to speed development
 - Guidances on innovative approaches: Adaptive Trial Designs, Use of Meta-Analysis Tools
 - Drug Development Tools:
 - Patient-Reported Outcomes, Biomarkers, Animal Models
 - Meetings targeted at supporting innovation



Role of the Regulator: Supporting Continued Progress

- Invest in appropriate collaborative partnerships: interdependence is the reality
 - Broaden the conversations beyond usual partners and topics for models and expertise
- Acknowledge differences exist (e.g., between regulators, regulations, needs, values)
- Build opportunities to harmonize existing knowledge, databases and standards
- Be prepared to question assumptions

WARNING



**CHALLENGES
AHEAD**

Summary/Conclusions

- This is a transformational time in healthcare. Expectations, resources, and challenges all changing
- FDA has a clear and understood role to support our public health mission, including the need to support change and innovation, while remaining true to our historic mission
 - Transparency, focus, collaboration, and flexibility are essential for success



- The art of progress is to preserve order amid change and to preserve change amid order

---Alfred North Whitehead

