Advancing Regulatory Science and Innovation for Public Health

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Overview

- Regulatory Science: What and Why?

- FDA's Advancing Regulatory Science Strategic Plan, Priorities and Representative Projects, including Collaboration and Partnerships

What is Regulatory Science?

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

    - *A bridge between basic/translational science and products*

    - *Includes the tools required for assessing risks and benefits*

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

Regulatory Science at FDA - Why?

- Major investments and advances in basic science not efficiently translating to products for patients

- Product development is lengthy (time is money), increasingly costly, and success rates have been low – though we are seeing change

- Failure often related to predictive science evaluating efficacy and/or safety

- Product development/evaluation tools and approaches have not kept pace with or incorporated emerging technologies – a major need and opportunity

- FDA is involved throughout product life cycles, sees products across classes/diseases, and can contribute intellectual capital to recognizing and solving regulatory science gaps, including through collaboration

- *All approaches used to estimate risk can be strengthened and estimates made more accurate when uncertainties in underlying findings and assumptions are reduced*
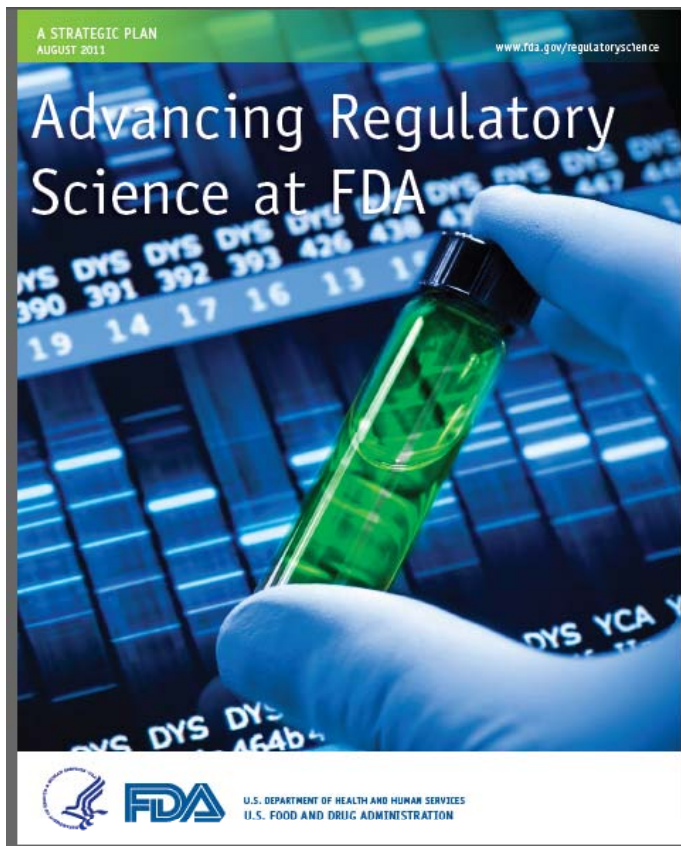
FDA Strategic Plan for Regulatory Science

VISION

FDA will advance regulatory science to speed innovation, improve regulatory decision-making, and get safe and effective products to people in need. 21st-century regulatory science will be a driving force as FDA works with diverse partners to protect and promote the health of our nation and the global community.

Eight Strategic Priority Areas
1. Transform Toxicology to Enhance Product Safety

Vision: *Advances in life sciences and engineering transform product evaluation, better identifying and predicting risk – and reducing animal testing*

- Develop better models of human adverse response

- Identify and evaluate toxicity biomarkers and endpoints

- Develop and use computational methods and *in silico* modeling

Priority Area 1:
Example: "Human on a Chip"

Challenge: Toxicity still a major issue in medical product development - preclinical testing relies largely on animal studies that:

- Are expensive and time consuming

- Don't always reliably predict toxic effects in humans, or who will be affected

- Don't provide information about genetic differences in toxicity within human populations

- Also frequently generate false alarms with result that promising products, which may be safe for all or some of the population, are abandoned
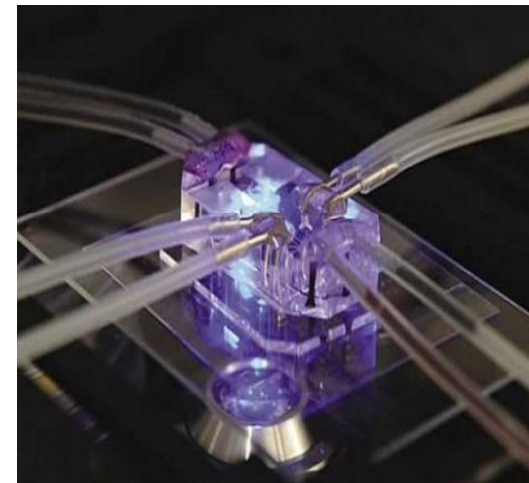
Human on a Chip *(cont)*

Solutions: FDA/DARPA/NIH supporting development of systems for better prediction of human toxicity/effectiveness. Tool links multiple organ-like systems to:

- Observe effects on interacting systems simultaneously
- Engineer models to mimic disease states or that use cells with specific genetic backgrounds relevant to diseases and/or drug interactions
- Screen and test for both toxicity and potential benefit

Benefits

- Identify toxicity (*and non-toxicity*) earlier, protect patients, lower costs
- Speed treatments to patients in need – more safely
- Provide relevant *in vitro* models when disease doesn't occur naturally or is difficult to study (e.g. for medical countermeasures, rare disorders)

–*In vitro and computational toxicology are a potential area for collaboration between FDA and global colleagues. Under discussion with JRC*

2. Stimulate Innovation in Clinical Trials and Personalized Medicine to Improve Product Development and Patient Outcomes
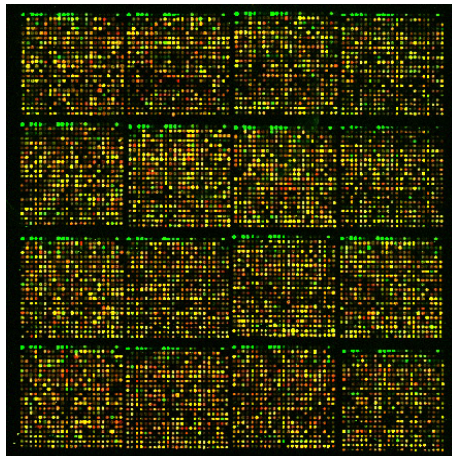
Vision: Product development is radically different – agile and adaptive as new information is collected, bringing clinical and biologic information together to identify population subgroups and individuals who will uniquely benefit, and bringing products to patients more rapidly, efficiently and safely

- Identify and qualify new biomarkers
- Develop and refine clinical trial designs, endpoints, and analysis
- Leverage existing and future clinical trial data, including complex biologic data, and in individualizing treatment

Example: Methods to Screen New Drugs for Harmful HLA-based Interactions

- **Challenge:** Several rare, serious adverse drug reactions are linked to HLA gene variants, but with little mechanistic understanding to allow prediction/prevention

- **Seeking Solution:** FDA developed a model of drug-induced autoimmunity in which abacavir alters quantity and nature of self-peptide loading into HLAB*57:01, generating neoantigen peptides that drive polyclonal T-cell autoimmunity and multiorgan toxicity.

- **Public Health Benefit:** The methods and assays developed can now also be applied to screen new drugs for HLA interactions and to predict and protect at-risk patients.

3. Support New Approaches to Improve Product Manufacturing and Quality

Vision: More agile, less expensive manufacturing with increased consistency and reduced barriers to changes in manufacturing and reduced needs to test final products, and enhanced supply chain safety.

- Enable development and evaluation of novel and improved manufacturing methods and new analytical methods
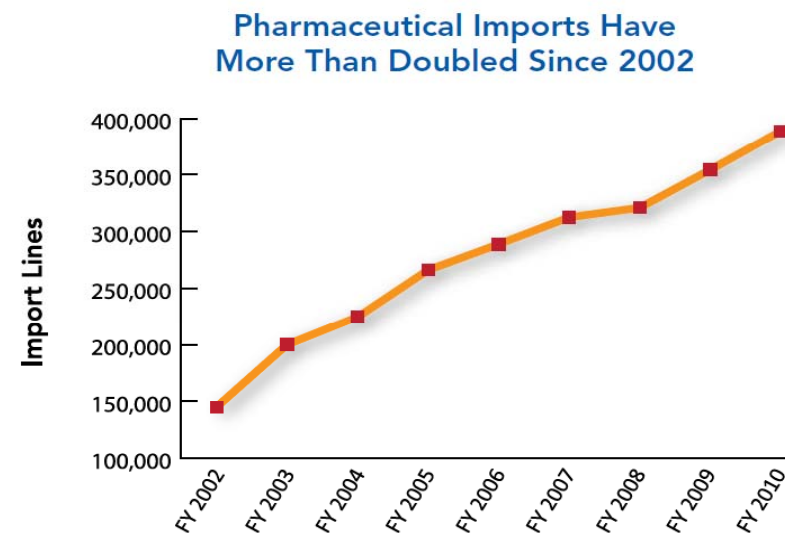- Reduce risk of contamination of products

Priority Area 3.
Example: FDA's Counterfeit Detection Device

Challenge:

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

Pharmaceutical Imports Have More Than Doubled Since 2002

Import Lines

400,000
350,000
300,000
250,000
200,000
150,000
100,000

FY 2002 FY 2003 FY 2004 FY 2005 FY 2006 FY 2007 FY 2008 FY 2009 FY 2010

Priority 3:Counterfeit Detection Device *(cont)*

Seeking Solutions:

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

- 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
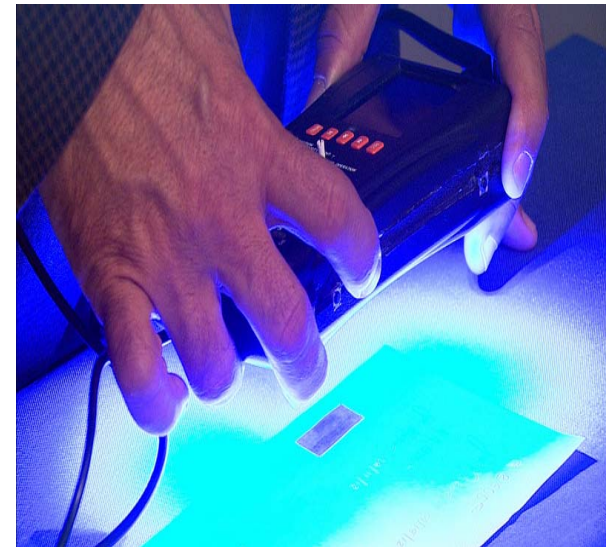
4. Ensure Readiness to Evaluate Innovative and Emerging Technologies

Vision: Stem cells, tissues and tissue engineered and combination products, new materials, and device technologies are successfully brought to bear against serious diseases and to repair and replace damaged organs and tissues.

- Stimulate development and create assessment tools for innovative products
- Ensure safe and effective innovation
- Coordinate regulatory science for emerging technology areas
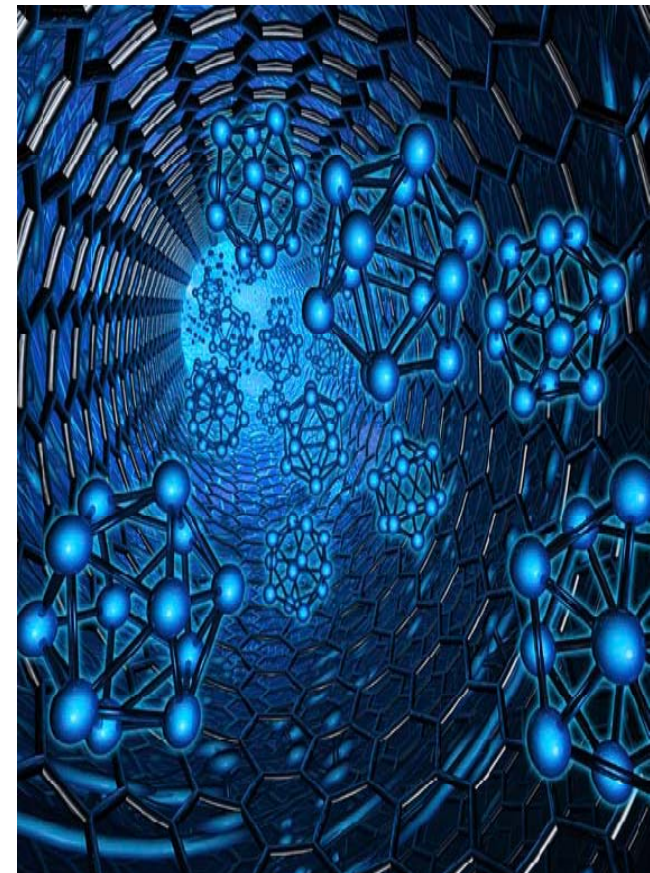
Priority Area 4: Example; The Virtual Family

Challenge: Evaluating novel devices using modeling has the potential to be more efficient and less expensive than current techniques.

Solution: FDA developed a computational "Virtual Family" based on high-resolution MRI scans of volunteers, including 80 different tissue types.

- The model enables study of how new devices interact in the body.
- FDA has used the Virtual Family to predict temperature and heating risk from radiofrequency and microwave radiation around implanted devices
- Benefits include reduced risks to patients and the potential to streamline device testing, including reducing animal use
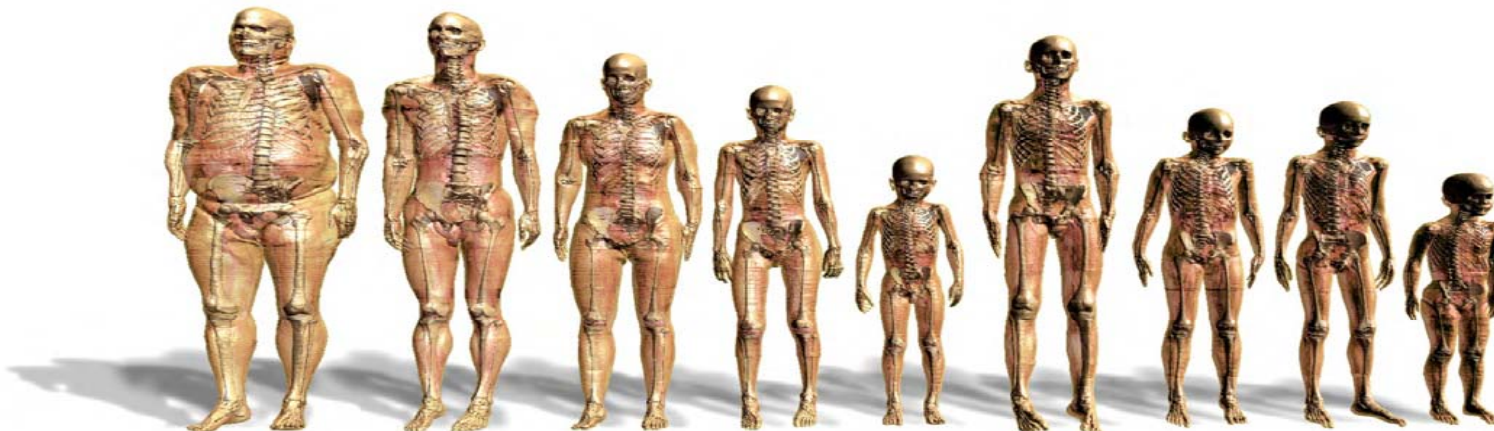

http://www.itis.ethz.ch/index/index_humanmodels.html

5. Harness Diverse Data through Information Sciences to Improve Health Outcomes

Vision: Vast amounts of clinical, health care and biological data are brought together and harnessed to speed product development and improve patient safety, outcomes and the effectiveness of health care

- Enhance IT infrastructure and data mining

- Develop/apply simulation models for product life cycles, risk assessment, and other regulatory uses

- Analyze clinical and preclinical data sets

- Incorporate knowledge from FDA files into database integrating a broad array of data types

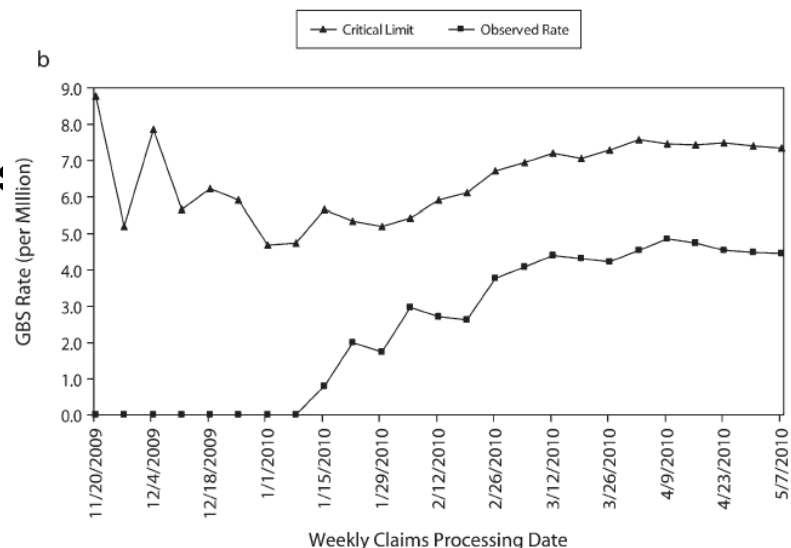- Develop new data sources, innovative analytical methods and approaches
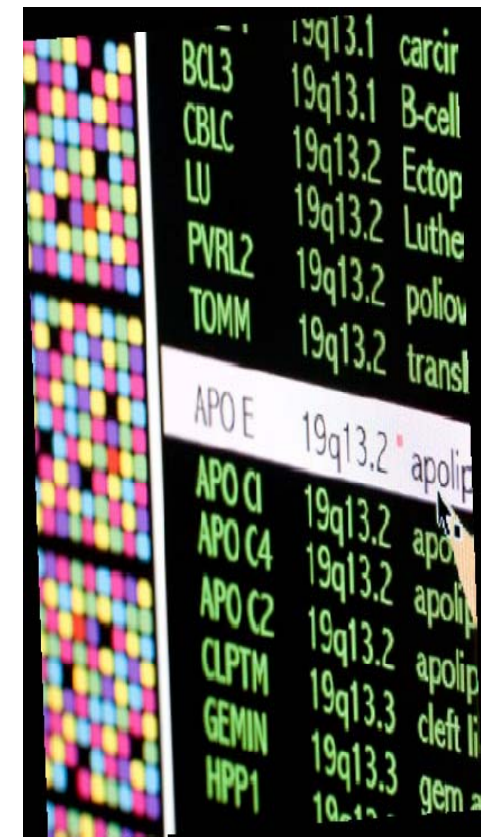
Priority Area 5 Example:
Real Time Safety Monitoring of 2009 Pandemic Vaccine

Challenge- In 1976 swine influenza outbreak, there was a marked increased rate of Guillain-Barre Syndrome (GBS) associated with vaccine. When the 2009 pandemic H1N1 virus was identified as of swine origin, there were concerns that the 2009 vaccine might cause GBS.

Solution

• FDA worked with partners in government and industry to rapidly capture and analyze health care data, including from 5 health systems with 38 million members, from CMS, and from 9 state/city immunization registries

• Real time analysis throughout the pandemic showed the vaccine was safe, and no unusual spike in GBS or other serious adverse effects, important information for the public and public health officials.

• Provided a model for data access and analytics for future public health emergencies & routine surveillance

b

Critical Limit   Observed Rate

GBS Rate (per Million)

9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

11/20/2009 12/4/2009 12/18/2009 1/1/2010 1/15/2010 1/29/2010 2/12/2010 2/26/2010 3/12/2010 3/26/2010 4/9/2010 4/23/2010 5/7/2010

Weekly Claims Processing Date

6. Implement New Prevention-Focused Food Safety System to Protect Public Health

- Assure mission-critical science capabilities
- Cultivate needed expert institutional knowledge and science base
- Improve information-sharing
- Establish and implement centralized planning and performance measurement

Priority Area 6.
Example: FDA 100K Genome Project

Challenge

- Each year an estimated 48 million Americans become ill from food borne disease, 128,000 hospitalized, 3,000 die

- Highly complex production and supply chains, including increased imports, mean outbreaks are frequent, evolve rapidly and can be widespread
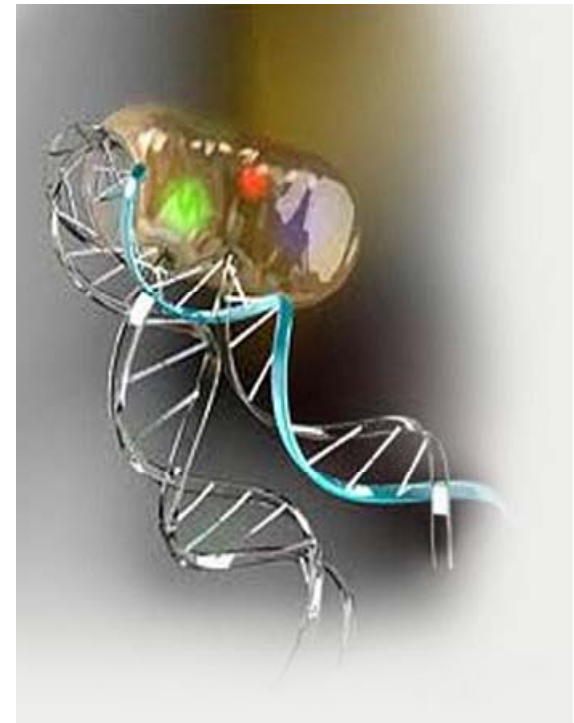
Priority Area 6.
Example: FDA 100K Genome Project

Seeking Solution

– FDA launched a 5-year public-private partnership with UC Davis and Agilent Technologies to develop a database with sequences of 100,000 pathogens. Next generation sequencing offers potential to:

  • Much more quickly and accurately identify outbreaks and track their source and spread

  • Better understand pathogens, including biology, virulence and how and where they are maintained in the environment

Public Health Benefit

– The 100K Genome Project will provide much needed tools and data to more rapidly identify sources of contamination, bring outbreaks under control, and prevent future outbreaks through more effective surveillance and public health interventions

Priority Area 6.
Example: New Method Detects Arsenic Risk from Feed

Challenge

•Roxarsone, an organic arsenical, used in animal feed for decades to prevent infection; approved for use in broilers, turkeys, and swine

•Inorganic arsenic species carcinogenic; organic generally safe

•Available data suggested Roxarsone resulted in primarily organic residues but information on metabolism to inorganic was limited

•Questions raised about potential for transformation to inorganic As
**Solution**

•FDA's Food Safety and Forensic Chemistry Centers collaborated to develop a method for As speciation for use in tissues that enables small amounts of carcinogenic inorganic arsenic to be identified in presence of large amounts of organic arsenic

•Inorganic As was detected in treated fowl, resulting in withdrawal of product from market, and reduction of human As exposure

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Priority Area 6.
(cont)

Inductively Coupled
Plasma-Mass
Spectrometry (ICP-MS)

Liver extracts

20 ppb fortified liver
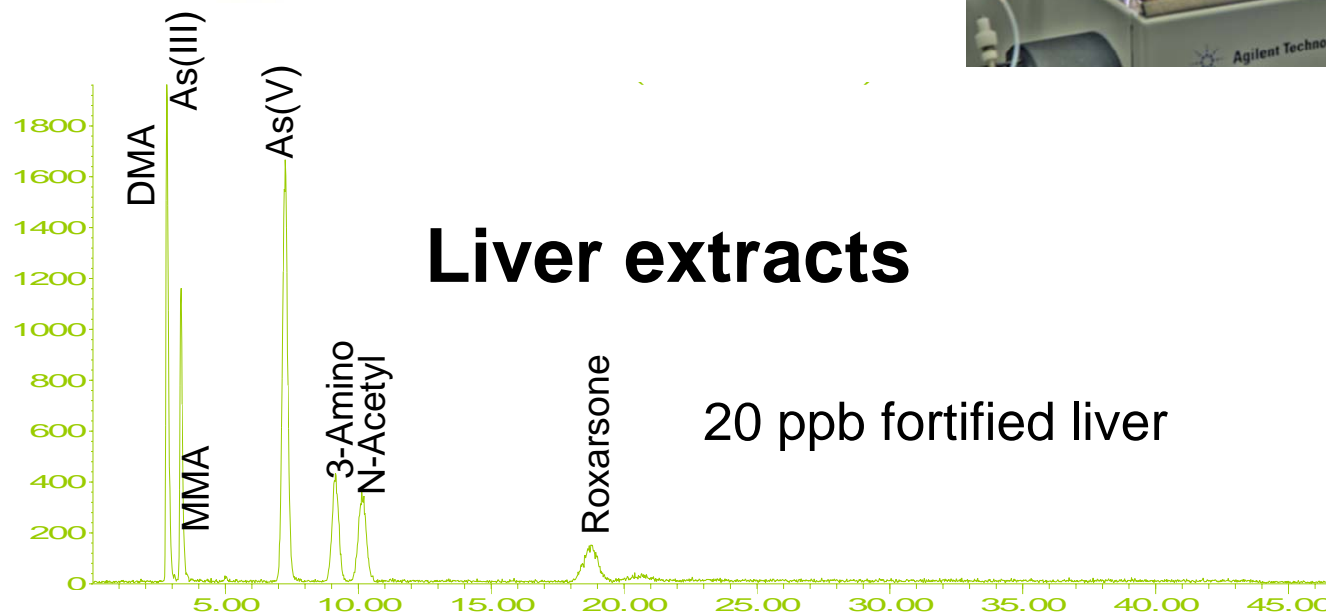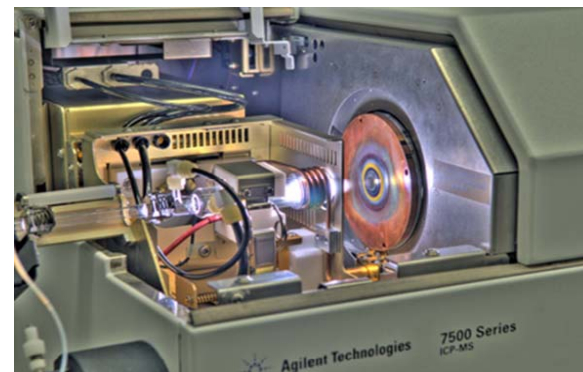
7. Facilitate Development of MCMs to Protect U.S. and Global Health and Security

Vision: The potential of innovation is realized to prevent and treat disease and reduce suffering globally, mitigate pandemics, and detect and rapidly respond to emerging infectious disease threats and bioterrorism.

- Modernize tools to evaluate MCM product safety, efficacy, and quality
- Develop and qualify biomarkers of diseases or conditions
- Enhance emergency communication

Priority Area 7.
Example: Ensuring effectiveness of vancomycin stockpiled for treating infectious diseases

Challenge - Vancomycin is an important antibiotic for treating resistant bacterial pneumonia. Reports questioned quality and efficacy of generics, which would have implications for the US Strategic National Stockpile

Solution - FDA/NIH/Institute for Therapeutic Innovation at U. of Florida evaluated vancomycin HCl for impurities, particularly crystalline degradation product-1 (CDP-1). FDA also assessed *in vitro* potency, and *in vivo* efficacy

Results - All five generic vancomycin HCl products were potent, effective *in vitro* and *in vivo* and also met USP specifications for purity; identified impurities were either degradents or derivatives of vancomycin B
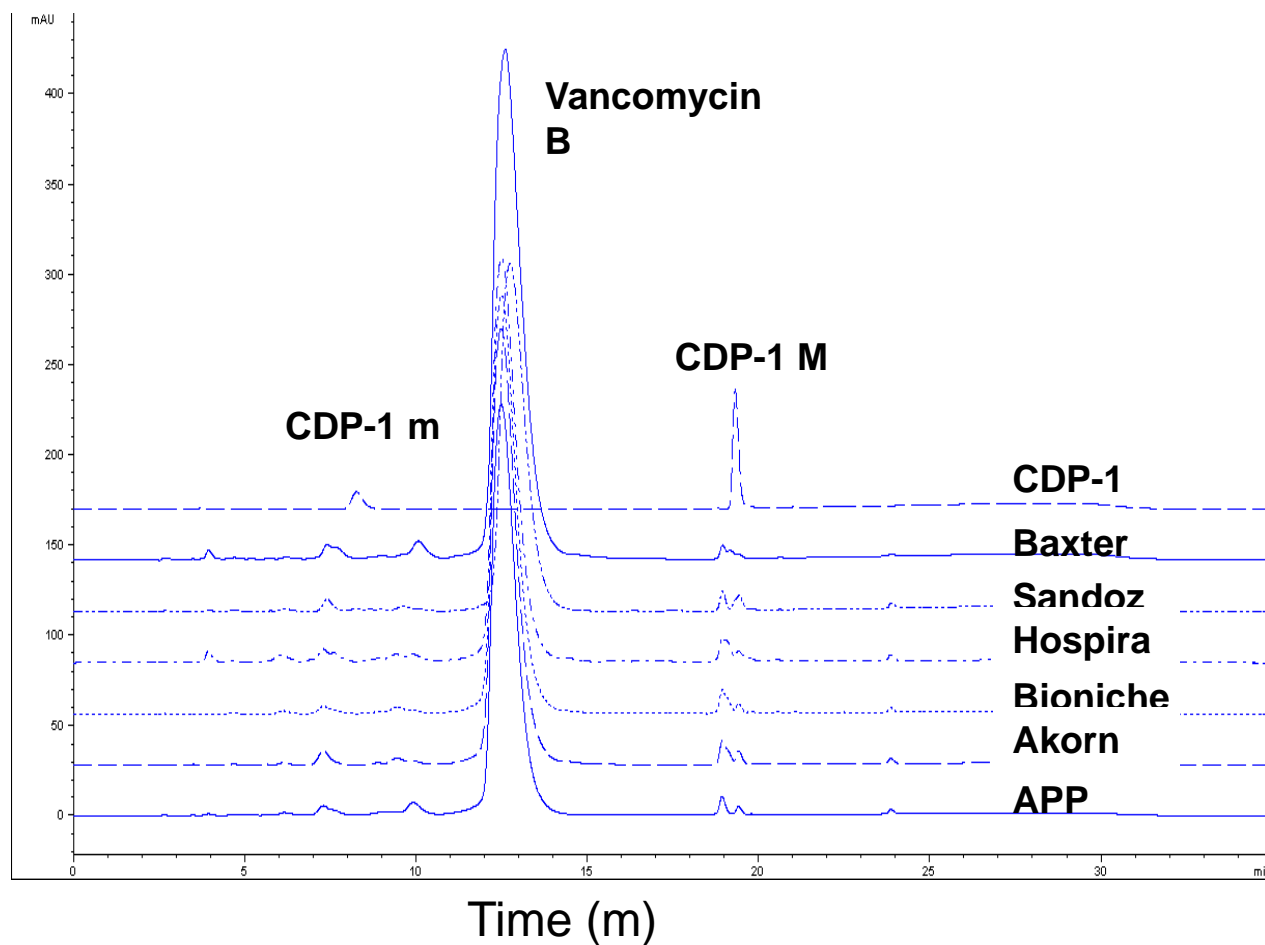
- – Based on these studies, we have confidence in our stockpiled vancomycin

Priority Area 7.
Example: Ensure effectiveness of vancomycin *(cont)*
LC Analysis of Vancomycin HCl

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8. Strengthen Social and Behavioral Science to Help Consumers and Professionals Make Informed Decisions

Priority Area 8.
Example: Population Assessment of Tobacco and Health (PATH) Study

PATH
Population Assessment
of Tobacco and Health

Challenge

- Smoking accounts for ~ 443,000 deaths in the U.S. annually – the leading cause of preventable death.

- 8.6 million users developat least one serious illness due to smoking.

- More than 3,800 American youth a day smoke their first cigarette.

- New forms of tobacco products are entering the marketplace.

Priority Area 8.
Example: PATH Study *(cont)*

PATH
Population Assessment
of Tobacco and Health

Seeking Solution

•FDA/NIH conducting Population Assessment of Tobacco and Health Study. (PATH Study), large, national, longitudinal cohort study of tobacco use and health that will measure tobacco use behaviors and related health effects.

•PATH Study baseline data collection ~ 59,000, in Autumn 2013, with a cohort of never, current, and former users of tobacco products age 12 and older. Cohort will be followed annually.

Public Health Benefit

•Results will be used to inform and assess tobacco regulations, including tobacco product standards, health warnings, marketing and advertising of new or modified risk products, and FDA public health campaigns

Partnerships and Collaboration

- Today's challenges are too complex for any one party, sector or nation to solve

- Urgent public health situations have *required* robust public-private 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

Power of PPP's:
Examples of FDA Engagement

- H1N1 (including global regulatory collaboration) and West Nile Virus responses
- Biomarkers Consortium – 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 – FDA, NIH, industry, patients
  - Standardizing imaging methods, identifying predictive host genetic and CSF biomarkers
- Coalition Against Major Diseases – FDA, patients, industry
  - Data standards and early identification of neurodegenerative disease
- Microarray Quality Consortium – industry, government

Partnering with Academia
Example: Centers of Excellence in Regulatory Science and Innovation (CERSIs)

- CERSI's bring cutting edge expertise and research capacity to FDA and the perspective and experience FDA brings to the collaborations helps ensure that the work in academia is useful for making sound regulatory decisions.
- U. Maryland: projects include studies of membrane transporters in drug development; innovative and emerging technologies like laser-based therapeutic devices and advanced tissue engineering; and better use of information to improve prescription drug use.
- Georgetown University: projects include collaborative research on pharmacogenomics, modeling autoimmune disorders, benefits and barriers to data-sharing among product researchers and developers
- Industry engaged through the FDA academic partners as well

# Reminders in a Moment of Anti-regulatory Zeal?

- While we all work to enable innovation and new technologies, and bear in mind that nothing is absolutely safe, sound regulation remains important to protect the public's safety, and to maintain confidence in industry and public health

- There are also health care and human costs of ineffective or marginally effective products (which can also displace the use/study of more effective therapy) - so lack of efficacy can be both a safety and economic issue

- Horse named Jim – started it all

- Thalidomide, sulfonamide, melamine

- Pharmaceutical compounding

Thanks – And a Call to Action

- Advancing regulatory science is critical to provide the tools needed to enhance the success of the biomedical enterprise.

- FDA has identified 8 priority areas where there are major opportunities to enhance how products are developed, evaluated and used.

- This work is too complex for any one party or sector. New collaborative models, including increased global collaboration, are essential for success.

- Such partnerships are WIN-WIN-WIN – for governments, innovators and, especially, for patients and global public health

- We are seeing progress!
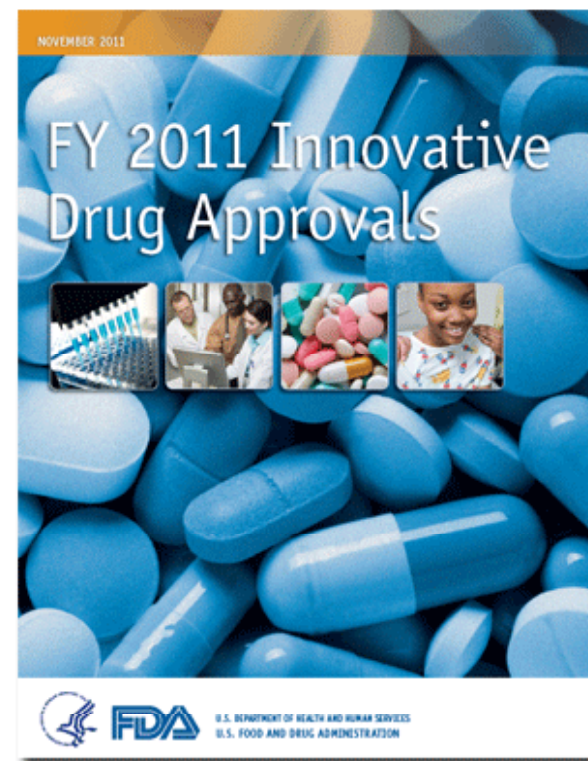
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