Importance of Regulatory Science

Driving Biomedical Innovation by Advancing Regulatory Science at FDA

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Industrial R & D Landscape

- Past 2010, biomedical research is in excess of $186 billion in R&D*
- The average cost of bringing a drug to market rose to more than $1 billion past 2011
- Medical Innovation sector employs nearly 1 million people **
- Biopharma industry indirectly contributed more than $300 billion to US GDP^
- Patent cliff (89.5B revenue lost) – US accounts for more than 40% of the word's patents in biotech
- Decrease productivity of R&D pipelines
  - by 20% (2001-2007)#
  - Increase in clinical trial cost

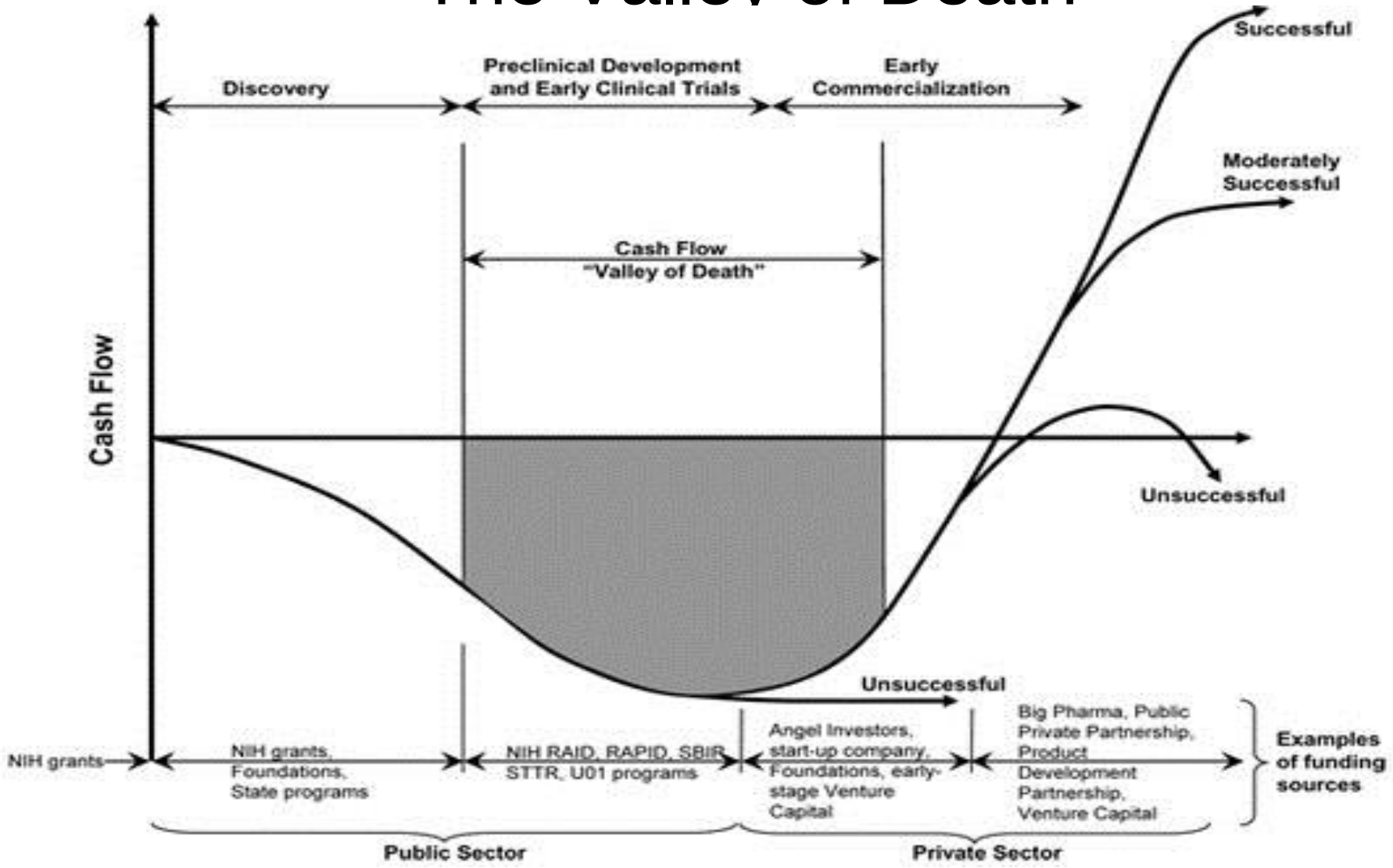
*http://www.researchamerica.org/uploads/healthdollar10.pdf

**NIH study: An Economic Engine

^PhRMA 2011

#Mckinsey quarterly 2/2012

The Valley of Death



Source: Steinmetz, K, Spack, E. The basics of preclinical drug development for neurodegenerative disease indications. *BMC Neurology* 2009; 9(Suppl 1):S2

REPORT TO THE PRESIDENT ON PROPELLING INNOVATION IN DRUG DISCOVERY, DEVELOPMENT, AND EVALUATION

Executive Office of the President

President's Council of Advisors on Science and Technology

SEPTEMBER 2012

The report concludes there are two critical needs:

1. Scientist need better methodologies and tools for translating basic biological insights into validated therapeutic targets and leads -- a gap in the drug discovery and development pipeline that academic scientists often view as “too applied” and pharmaceutical companies often see as “too basic” to justify private investment

The report concludes there are two critical needs, cont:

2. Pharmaceutical developers and regulators need to incorporate new efficiencies into clinical trials of candidate medicines – complex and costly human studies that today constitute 40% of the biopharmaceutical industry's R&D budget

Recommendations from PCAST report

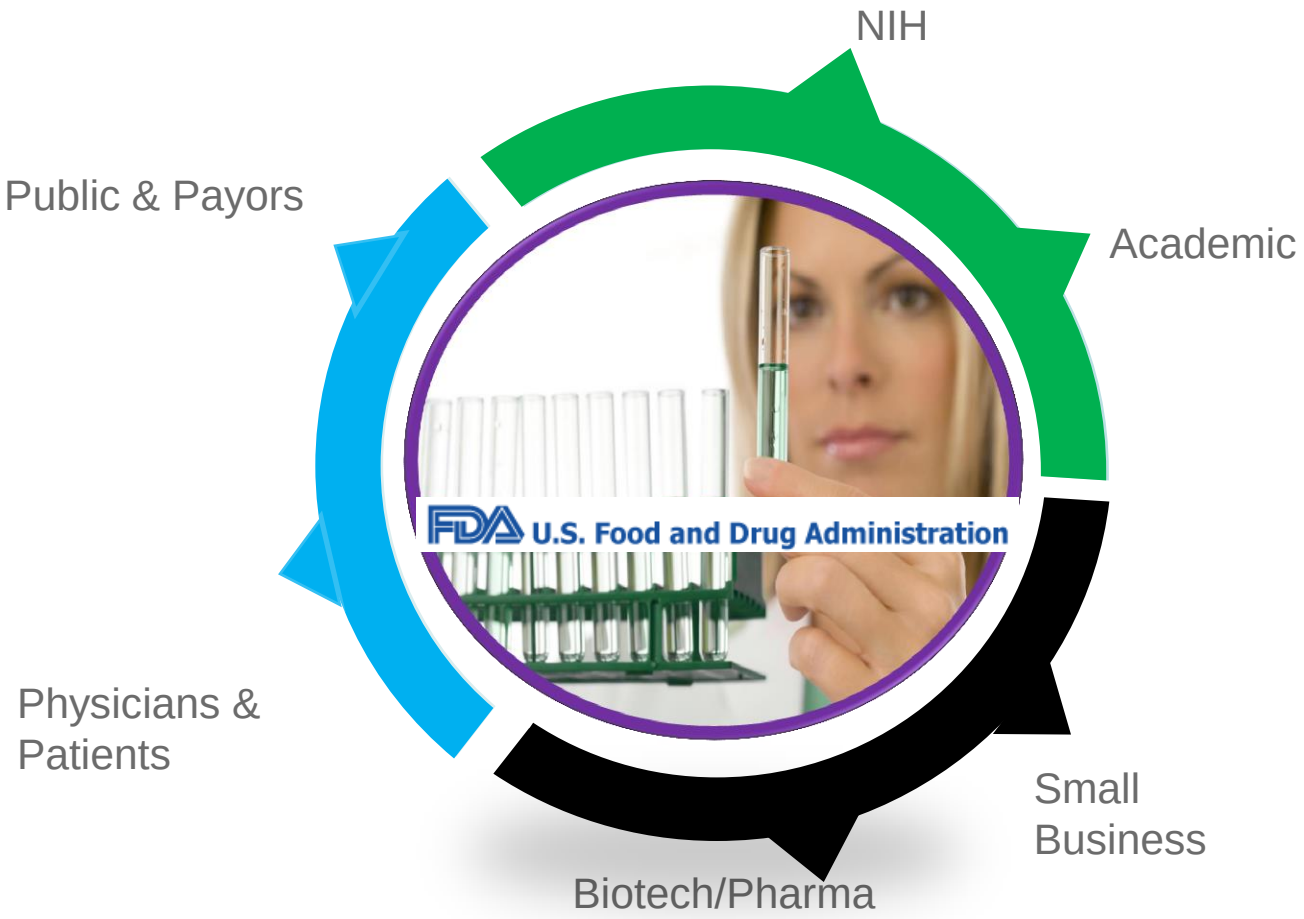
- Support Federal Initiatives to Accelerate Therapeutics
- Catalyze the Creation of a Broad-based Partnership to Accelerate Therapeutics
- Expand the Use of Practice of FDA's existing Authorities for Accelerated Approval and for Confirmatory Evidence
- Create a New Pathway for Initial Approval of Drugs shown to be Safe and Effective in a specific Subgroup of Patients
- Explore Approaches for Adaptive Approval via Pilot Projects under existing Pathways
- Improve FDA's Tool for Monitoring and Communication of Clinical Benefits & Risks
- Reform Management Practices at FDA
- Study Current and Potential Economic Incentives to Promote Innovation in Drug Development

FDA Mission

- FDA is responsible for protecting public health by:
  - Helping to speed innovations that make regulated products safer and more effective
  - Ensuring the public has accurate, science-based information on how to use medicines, devices, and food to improve their health
  - Regulating the manufacture, marketing, and distribution of tobacco products and reducing tobacco use by minors
  - Addressing the Nation's countermeasure capability and ensuring the security of the supply of food and medical products.

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.

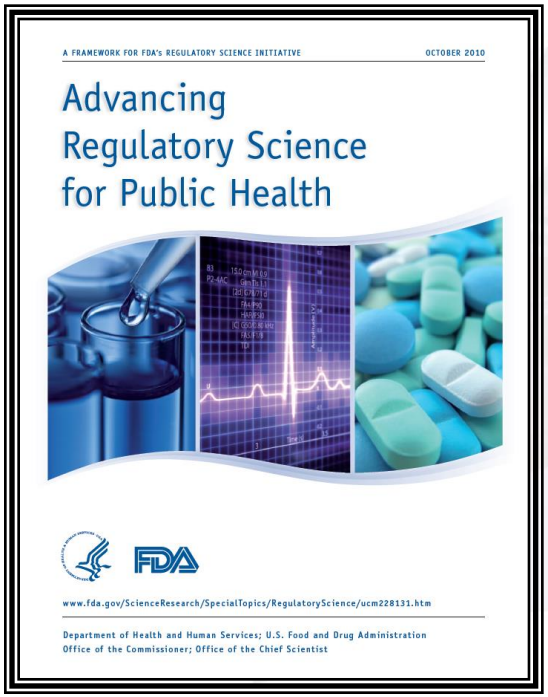


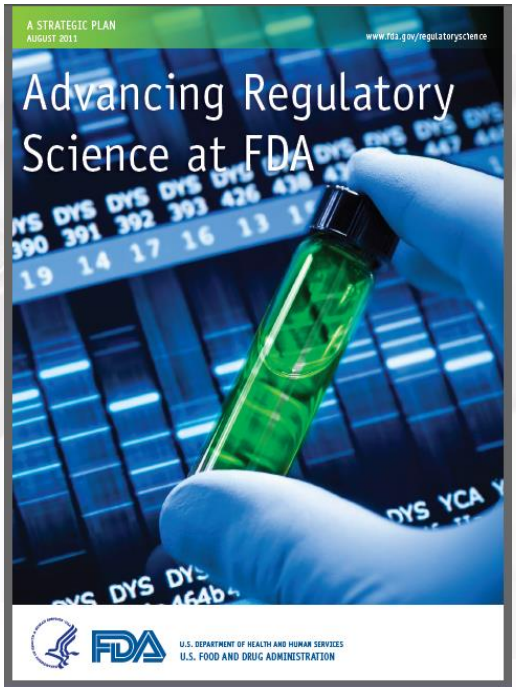
What is Regulatory Science?

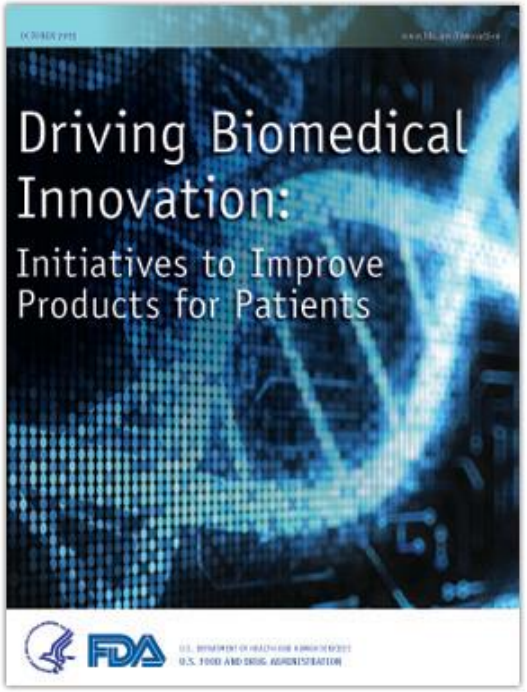
- The science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products
- The critical bridge between the “too basic” scientific research discoveries and “too applied” science of manufacturing and marketing of regulated products
- Includes areas of preclinical and clinical research, manufacturing, processing, and translational science in a product development and approval process (“the cycle”)
- May improve regulatory affairs processes


Discovery
Clinical Trial
Product on Market
Patients
Redefine patient as co-researcher
Reverse engineer to drive smarter basic research and product development
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
Stratify patients by:
• Genetics
• PRO's
• Behavior
• Disease definition
Better performance and outcome

Regulatory Science Publications







Innovation is a Core FDA Mission

Strategic Plan - Purpose

- 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

Eight (8) Priority Areas

- **Modernize Toxicology to Enhance Safety**

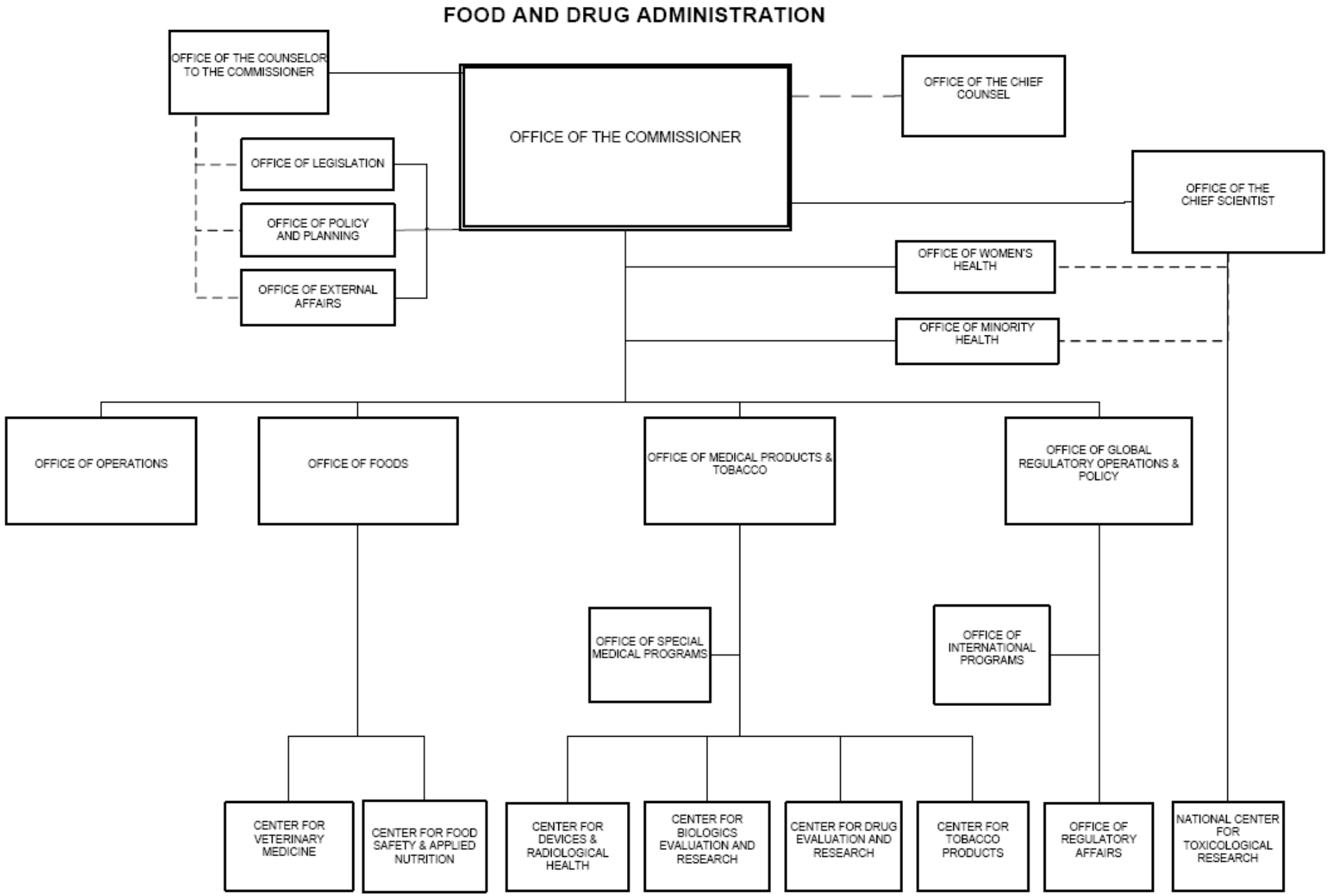
- **Stimulate Innovation in Clinical Evaluation & Personalized Medicine**
- **Support new Approaches to Improve Product Manufacturing and Quality**
- **Ensure FDA Readiness for Emerging Technologies**

- **Harness Diverse Data through Information Sciences to Improve Health Outcomes**
- **Enable a Prevention Focused Food Safety System**

- **Facilitate Development of MCMs to Protect US and Global Health and Security**
- **Strengthen Social and Behavioral Science to Help Consumers and Patients Make Informed Decisions**

Regulatory Science at FDA: Pillars in Implementation

- Leadership, coordination, strategic planning and transparency to support science and innovation
- Support for scientific excellence, professional development and a learning organization
- Support for mission-critical applied research, both at FDA and collaboratively
- Recruitment and retention of outstanding scientists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CENTER FOR FOOD SAFETY & APPLIED NUTRITION
CENTER FOR DEVICES & RADIOLOGICAL HEALTH
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH
CENTER FOR DRUG EVALUATION AND RESEARCH
CENTER FOR TOBACCO PRODUCTS
OFFICE OF REGULATORY AFFAIRS
NATIONAL CENTER FOR TOXICOLOGICAL RESEARCH

Office of the Chief Scientist

- Provide strategic leadership and support for high quality, collaborative, scientific activities that advance regulatory science and address important public health issues concerning FDA regulated products
- Lead agency efforts to protect and enhance scientific integrity
- Provide cross-center scientific coordination and research resources for all product areas
- Orchestrate the FDA Science Advisory Board, the Senior Science Council and the Critical Path Steering Committee in interactions with the Commissioner, the Directorates and the Center Directors.

Snapshot of Science Activities at FDA

- Scientific Publications (FDA-wide)
  2012 over 1,300 publications, several in Proc Natl Acad Sci, Science, Nature Reviews Genetics, Nature Biotech etc.
- Collaborations (examples)
  > 30 Government---CDC, USDA, NIH, NOAA, USGS, EPA etc
  > 90 Academic --- Univ. of Maryland, Virginia Tech, Mich. State, Howard Univ., Purdue, Univ. of Florida, UC Davis, Hopkins and other US & international centers
- Guidance Documents
  76 new guidance since 2011 for drugs
  >35 for biologics, >35 for medical devices, and 20 for food
- Infrastructures
  high throughput sequencing and analysis
  IT (high performance computing environment, bioinformatics)
- Workgroups, Consortia, and Committees

Critical Path and Regulatory Science Initiatives

- More than 40 CPI projects (from OCS, CBER, CDER, NCTR, CVM, CDRH)
- FDA collaborates with more than 25 organizations on CPI projects
- Clinical Investigator Training
- Research Areas
  - Biomarker/Trial design
  - Information Technologies/Bioinformatics
  - Toxicology and Modeling
  - Emerging Technologies
  - Manufacturing
  - Communication and Training

Centers of Excellence in Regulatory Science and Innovation

- FDA funded 2 awards for a duration of 3 years thus far
- Three Main Components:
  - Regulatory science collaborative research in FDA priority areas
  - Staff training and scientific exchange (bi-directional)
  - Core dedicated infrastructure for support
- FDA's Collaborating Centers of Excellence in Regulatory Science and Innovation (CERSI) Cooperative Agreement RFA awarded to Georgetown University and University of Maryland

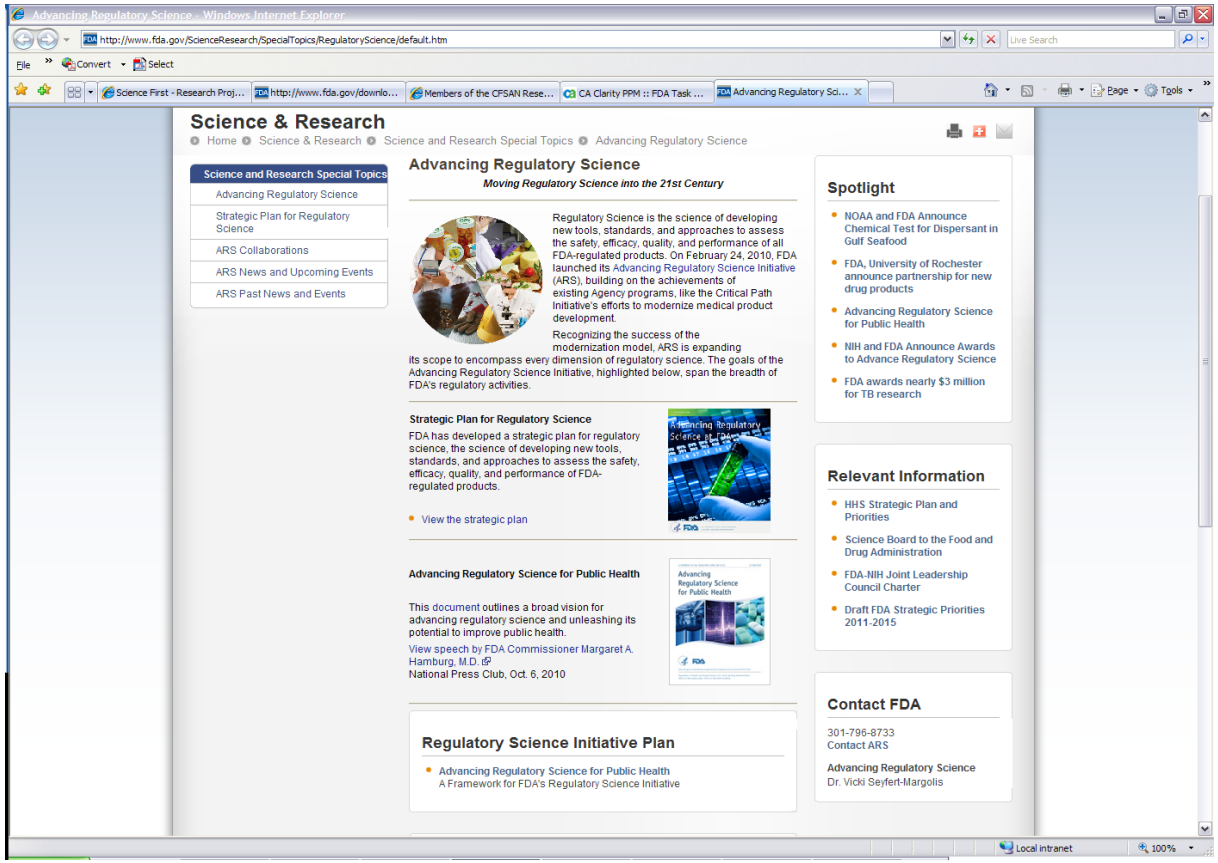
FDA Broad Agency Announcement FDABAA-12-00118

- Solicitation to encourage participation by science and technology based firms and educational institutions in meeting FDA goals for innovative ideas and approaches for regulatory science.

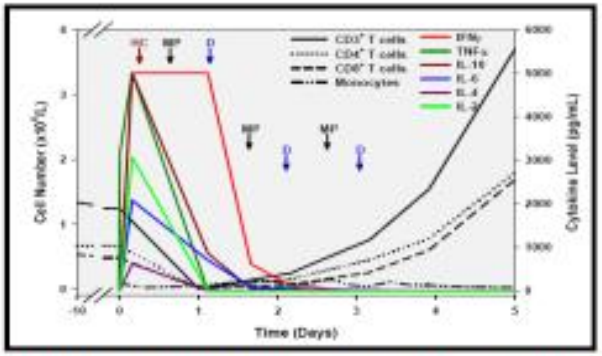
- Focus on FDA Advancing Regulatory Science Research Areas

Advancing Regulatory Science Website

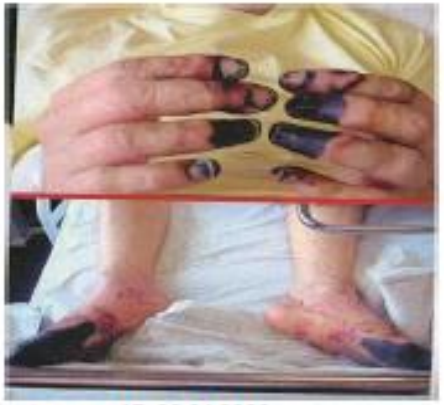
[Click Here to visit site.]



Acute Cytokine Release Syndrome – nightmare of clinicians, toxicologists and developers



Data from the TGN1412 trial (Suntharalingam, NEJM, 2006)



stern no. 17, 20.04.2006

- **Unpredicted <u>cytokine storm</u>** can be catastrophic to patients, researchers, products and companies (TGN1412).
- Even more to be considered in the future: **>250 mAb in development** (ref: insightpharmareports.com)
- **Cytokine release** is associated with clinically relevant infusion/administration related reaction (IRR/ARR) upon first exposure, BUT:
  - can be part of effector MoA (e.g. oncology)
  - can better be handled clinically, if predicted

A clinicians' primary safety concerns for biologics: a ranking

- **Acute ARR/IRR – application/infusion related reactions**
  - cytokine storm, non-hypersensitivity reactions (non-HSR)
- **Acute blockage of capillaries by immune complexes**
  - HSR Type III – IgG mediated complement activation with organ failure and coagulation system dysregulation (ADA independent possible)
- **Acute systemic reactions of hypersensitivity mediated by ADA**
  - HSR Type I mediated by IgE, immediate type
  - HSR Type II IgG or M mediated ADCC or complement-mediated cell lysis
- **Injection site reactions**
  - possible involvement of HSR Type IV – Th cell mediated, delayed
  - local allergic reaction unrelated to therapeutic Ab
- **Immunogenicity (ADA) adversely affecting PK, PD and efficacy**
- **Toxicity – long term**

Product safety impact factors

- Product specifications/manufacturing process/contaminations
- Dose/concentration, treatment regimen/duration/interval, route of application,
- Bio target, PK, PD, ADA/immune status
- Indication/disease group, concomitant-meds, individual factor/polymorphism

If it were not for the great variability among individuals, medicine might as well be a science and not an art.
Sir William Osler (1849 - 1919)

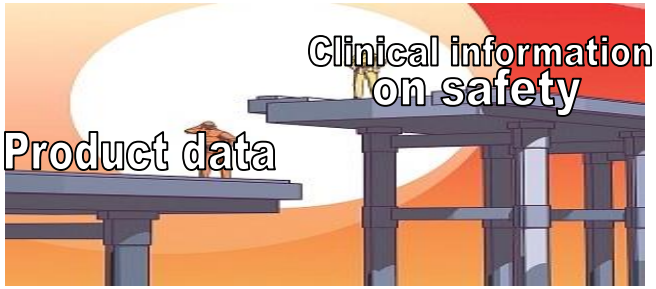
Product contaminants

- Host cell proteins
- Host cell DNA
- In-process “impurities”, including pyrogens, microbes
- Leachables
- Aggregates and particles
- Denatured, fragmented and chemically altered proteins
- Non-human glycoforms
- Degraded excipients

Current approaches to product safety and desired future: **We need better medical product development tools**

- **Current common approach**:
  - Product process and quality controls do not directly correlate with clinical safety
  - Animal tox studies possibly irrelevant for safety predictions
  - Phase I-IV clinical studies can reveal surprises

Gap in understanding of clinical data



- **Desired future:**
  - Improve patient outcome and product safety
  - Address gaps between nonclinical and clinical data
  - Improve predictive tools for safety assessment
  - Minimize irrelevant animal studies and improve clinical studies

Potentially predictive tools (drug development tools) for the assessment of product safety

Predictive tools for consideration:

- *In silico*
- *In vitro*
- *In vivo* (animal models, transgenic & humanized mice)
- Human-on-a-chip

Problems:

- Inconsistency in clinical information collection and reporting (data standards)
- No databases to link research with clinical data and changes in quality attributes of the product (pre-competitive info sharing)
- Validation of method and clinical qualification (involving regulatory authorities)
- Resources

Information needed to define algorithms for "Tox Tools" in clinical qualification (validation as drug development tool)

Comprehensive databases of relevant information and availability of access

- **Alignment across developers, regulators, providers and patients needed to develop qualification of tools based on evidence for context of use**
  - available toxicology information
  - aggregate safety info
- **Consistency in nonclinical (tox) and clinical studies**
  - data collection (sufficient details in connections to adverse events)
  - interactive communications between tox, clinical and CMC areas
  - development of data standards
- **Comprehensive product information**
  - product knowledge databases
  - risk registers
  - pharmacovigilance
  - post marketing surveillance

THANK YOU





Questions

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