The Challenges of Implementing Innovations in Drug Development

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Or… What's a Regulator to Do?

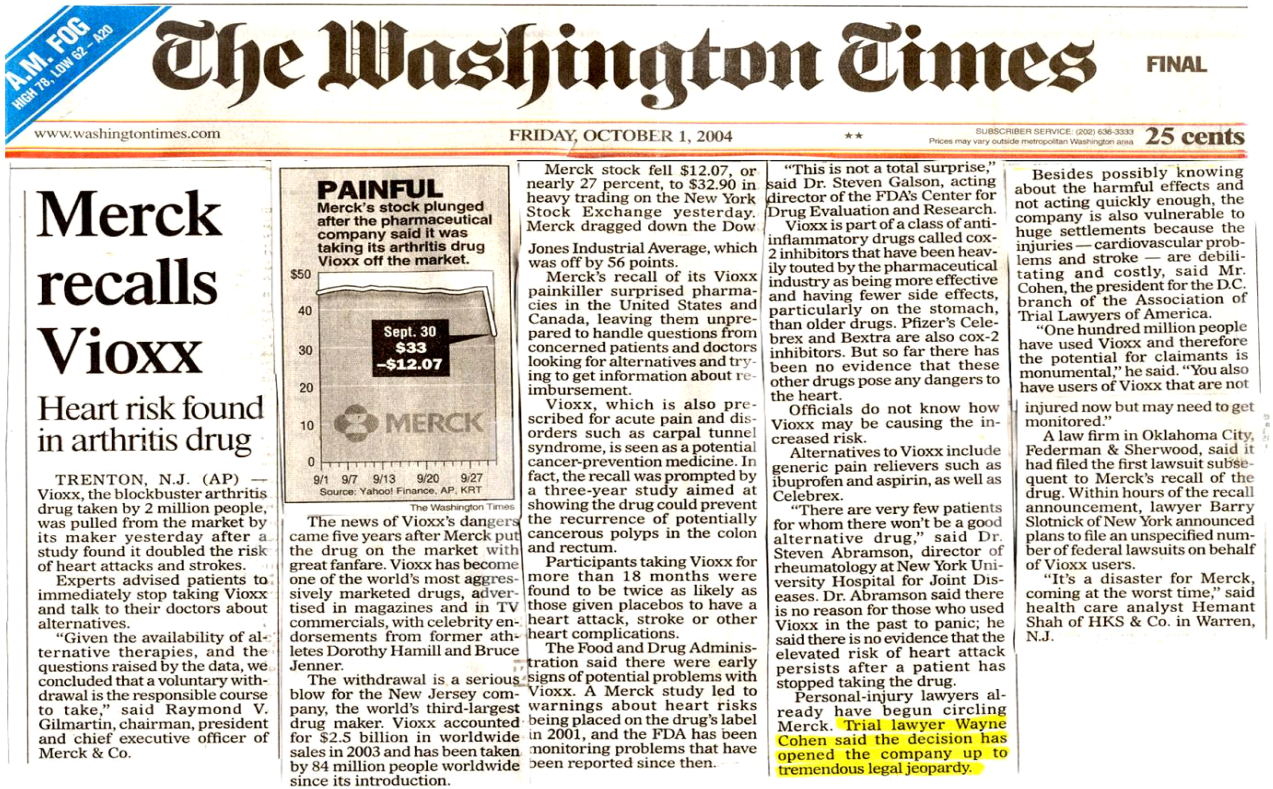
- Nature of the challenge
- Improving the efficiency of development through collaboration and communication
- Improving internal FDA processes to support new paradigms
- Staying open to change

Context: New Realities in the 21st Century

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

Increased Safety Focus

Unexpected Drug Safety Toxicity: Need Better Tools



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The Washington Times FINAL

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Merck recalls Vioxx

Heart risk found in arthritis drug

TRENTON, N.J. (AP) — Vioxx, the blockbuster arthritis drug taken by 2 million people, was pulled from the market by its maker yesterday after a study found it doubled the risk of heart attacks and strokes.

Experts advised patients to immediately stop taking Vioxx and talk to their doctors about alternatives.

"Given the availability of alternative therapies, and the questions raised by the data, we concluded that a voluntary withdrawal is the responsible course to take," said Raymond V. Gilmartin, chairman, president and chief executive officer of Merck & Co.

PAINFUL
Merck's stock plunged after the pharmaceutical company said it was taking its arthritis drug Vioxx off the market.

Source: Yahoo! Finance, AP, KRT
The Washington Times

The news of Vioxx's dangers came five years after Merck put the drug on the market with great fanfare. Vioxx has become one of the world's most aggressively marketed drugs, advertised in magazines and in TV commercials, with celebrity endorsements from former athletes Dorothy Hamill and Bruce Jenner.

The withdrawal is a serious blow for the New Jersey company, the world's third-largest drug maker. Vioxx accounted for $2.5 billion in worldwide sales in 2003 and has been taken by 84 million people worldwide since its introduction.

Merck stock fell $12.07, or nearly 27 percent, to $32.90 in heavy trading on the New York Stock Exchange yesterday. Merck dragged down the Dow Jones Industrial Average, which was off by 56 points.

Merck's recall of its Vioxx painkiller surprised pharmacies in the United States and Canada, leaving them unprepared to handle questions from concerned patients and doctors looking for alternatives and trying to get information about reimbursement.

Vioxx, which is also prescribed for acute pain and disorders such as carpal tunnel syndrome, is seen as a potential cancer-prevention medicine. In fact, the recall was prompted by a three-year study aimed at showing the drug could prevent the recurrence of potentially cancerous polyps in the colon and rectum.

Participants taking Vioxx for more than 18 months were found to be twice as likely as those given placebos to have a heart attack, stroke or other heart complications.

The Food and Drug Administration said there were early signs of potential problems with Vioxx. A Merck study led to warnings about heart risks being placed on the drug's label in 2001, and the FDA has been monitoring problems that have been reported since then.

"This is not a total surprise," said Dr. Steven Galson, acting director of the FDA's Center for Drug Evaluation and Research.

Vioxx is part of a class of anti-inflammatory drugs called cox-2 inhibitors that have been heavily touted by the pharmaceutical industry as being more effective and having fewer side effects, particularly on the stomach, than older drugs. Pfizer's Celebrex and Bextra are also cox-2 inhibitors. But so far there has been no evidence that these other drugs pose any dangers to the heart.

Officials do not know how Vioxx may be causing the increased risk.

Alternatives to Vioxx include generic pain relievers such as ibuprofen and aspirin, as well as Celebrex.

"There are very few patients for whom there won't be a good alternative drug," said Dr. Steven Abramson, director of rheumatology at New York University Hospital for Joint Diseases. Dr. Abramson said there is no reason for those who used Vioxx in the past to panic; he said there is no evidence that the elevated risk of heart attack persists after a patient has stopped taking the drug.

Personal-injury lawyers already have begun circling Merck. Trial lawyer Wayne Cohen said the decision has opened the company up to tremendous legal jeopardy.

Besides possibly knowing about the harmful effects and not acting quickly enough, the company is also vulnerable to huge settlements because the injuries — cardiovascular problems and stroke — are debilitating and costly, said Mr. Cohen, the president for the D.C. branch of the Association of Trial Lawyers of America.

"One hundred million people have used Vioxx and therefore the potential for claimants is monumental," he said. "You also have users of Vioxx that are not injured now but may need to get monitored."

A law firm in Oklahoma City, Federman & Sherwood, said it had filed the first lawsuit subsequent to Merck's recall of the drug. Within hours of the recall announcement, lawyer Barry Slotnick of New York announced plans to file an unspecified number of federal lawsuits on behalf of Vioxx users.

"It's a disaster for Merck, coming at the worst time," said health care analyst Hemant Shah of HKS & Co. in Warren, N.J.

Regulatory Actions due to Drug-Induced Liver Injury (DILI)*: 1995-2009*

Withdrawals	Warnings
bromfenac	acetaminophen, leflunomide
troglitazone	nefazodone, nevirapine
pemoline	pyrazinamide/rifampin, terbinafine
ximelegatran*	valproic acid, zifirlukast
lumiricoxib*	atomoxetine, interferon
Special Use	saquinavir, infliximab
trovofloxacin	bosentan, telithromycin
felbamate	erlotinib, natalizumab
tolcapone	kava, lipokinetix (DS)

**Non-US markets*

Drugs Removed From Market for Arrhythmia Risk

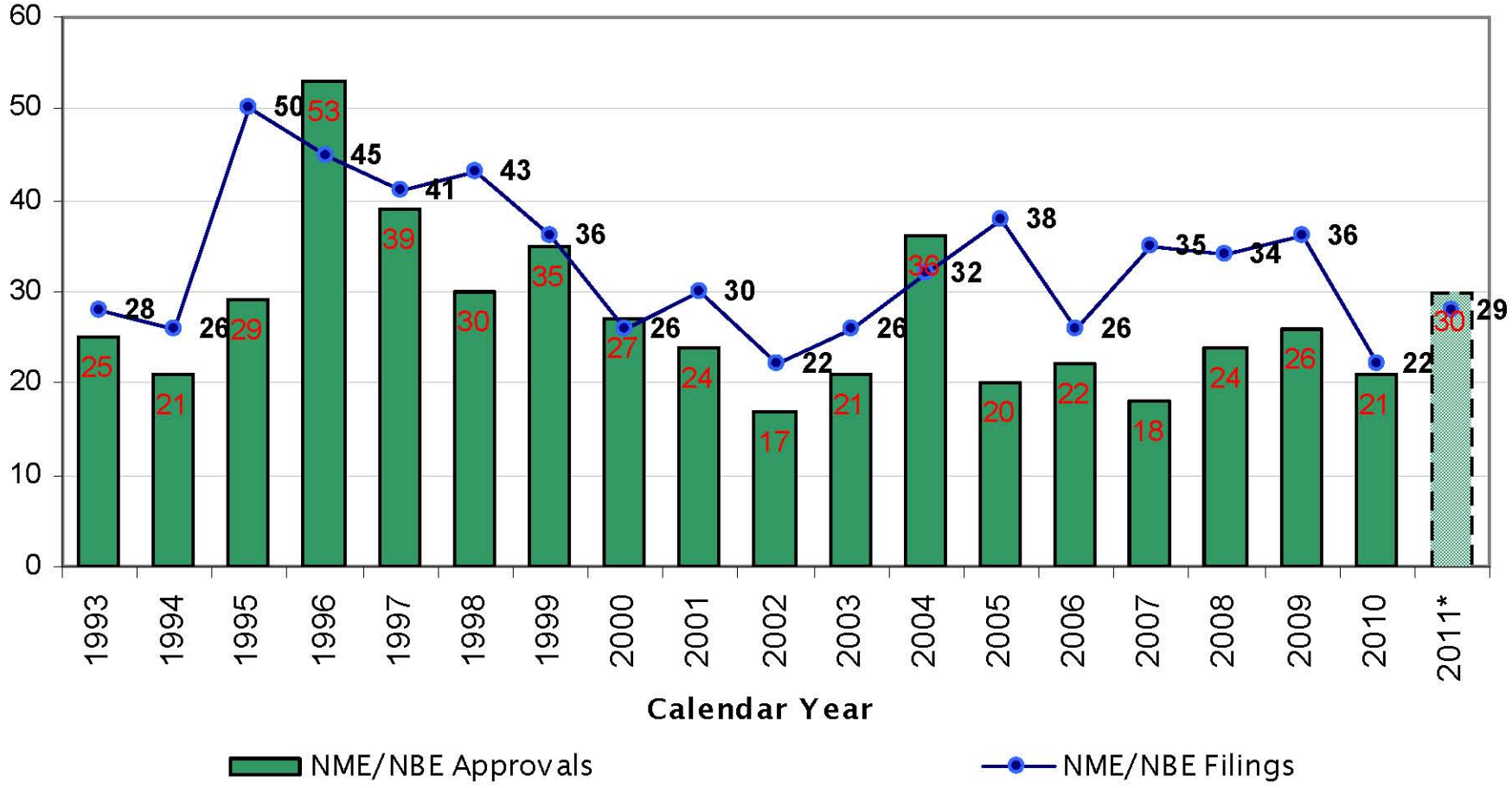
- **Encainide (Enkaid®)** **1991** (1986)
- **Terfenadine (Seldane®)** **1998** (1985)
- **Astemizole (Hismanal®)** **1999** (1988)
- **Grepafloxacin (Raxar®)** **1999** (1997)
- **Cisapride (Propulsid®)** **2000** (1993)
- **Levomethadyl (Orlaam®)** **2003** (1993)

*** year of removal (year of approval)**

Lagging Drug Development

- Basic science discoveries promise accelerating product development but delivery has lagged
- FDA is only one part of extremely complex healthcare system. Improving the science of drug development is challenging and requires collaboration

CDER New Molecular Entity and New Biologic Entity Filings and Approvals



*CDER data as of 11/30/2011. New Biologic Entities are included in CDER figures beginning in 2004, when review authority for therapeutic biologic products was transferred from CBER to CDER.

Outline: What's a Regulator to Do?

- Understand the nature of the issue
- Improve the efficiency of development through collaboration and communication
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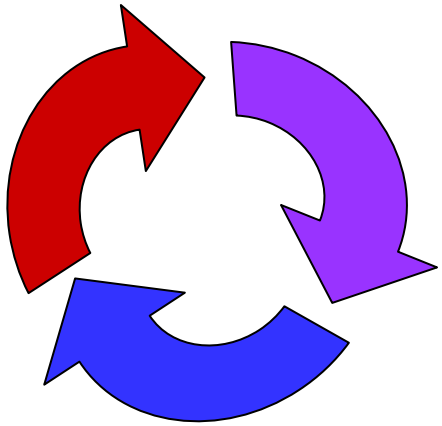
CDER: Focused on Core Business Functions

Pre-Market Review

Support for efficient product development. Assessment of safety and effectiveness of new pharmaceuticals



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

CDER

- 3,206 employees as of March 30th, >2,300 scientists and professionals:
  - 450+ MDs
  - 375+ Toxicologists
  - 350+ Chemists
  - 150+ Statisticians
- Director: Janet Woodcock

Improving Product Development Efficiency

Guidance and Communication

Collaboration

Regulatory Science Activities: Communication

- Provide clear roadmap to speed development
  - Guidances: Adaptive Trial Designs, Meta-Analysis, Adverse Events Reporting Rule
  - Drug Development Tools:
    - PROs, Biomarkers, Animal Models (CT)
  - PDUFA V proposal for enhanced communications teams to aide drug developers

Example of Regulatory Innovation: Adaptive Trial Design Guidance

- Adaptive Design Clinical Trials for Drugs and Biologics (2010)
- Goals:
  - Decrease time between discovery & “confirmatory” studies
  - Make studies more likely to succeed by adapting design elements that could not be fully known when the study was planned and powered:
    - effect size
    - event rate in the population
    - most responsive subset
    - the right dose
    - the best study endpoint

Regulatory Science Activities: Collaboration

Example: Supporting Use of Biomarkers

I-Spy 2: clinical trials to screen promising breast cancer drugs

- Biomarker Consortium--- public/private partnership: FDA / NIH / pharma co's
- Uses biomarkers from tumors to identify the most effective treatments by patient type

- Biomarker Consortium also working on new biomarkers for lymphoma, diabetes, renal disease, etc

Example: Developing Disease Models

Model	Objective	Status
Parkinson Disease	Derive endpoints to discern disease-modifying and symptomatic effects	-Completed; provided input to industry -Public meeting in April, 2008 -Manuscript Published
Non-Small Cell Lung Cancer (NSCLC)	Quantify tumor size and survival relationship to guide future drug development decisions	-Completed -Clinical Pharmacology AC meeting in March 2008 -Manuscript Published
Pulmonary Arterial Hypertension	Quantify hemodynamic-exercise tolerance relationship to guide approval in pediatrics	-Completed -Cardiorenal AC meeting in 2010 -Draft publication ready
HCV Disease Model	Quantify viral dynamics and drug effects to guide dose selection for new compounds	-Completed modeling -Communicated with industry -Manuscript published
Alzheimer's Disease Model	Quantify disease progression and evaluate competing trial designs and endpoint for disease-modification claims	-Completed modeling, manuscript submitted -Initiated trial simulations

PD, NSCLC: http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm167032.htm
PAH: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM220250.pdf
HCV: Jadhav PR.Antiviral Information Management System: a Prototype for Operational Innovation in Drug Development; *Journal of Clinical Pharmacology 50(9): 50S (2010)*

Example: International Serious Adverse Event Consortium (iAES)

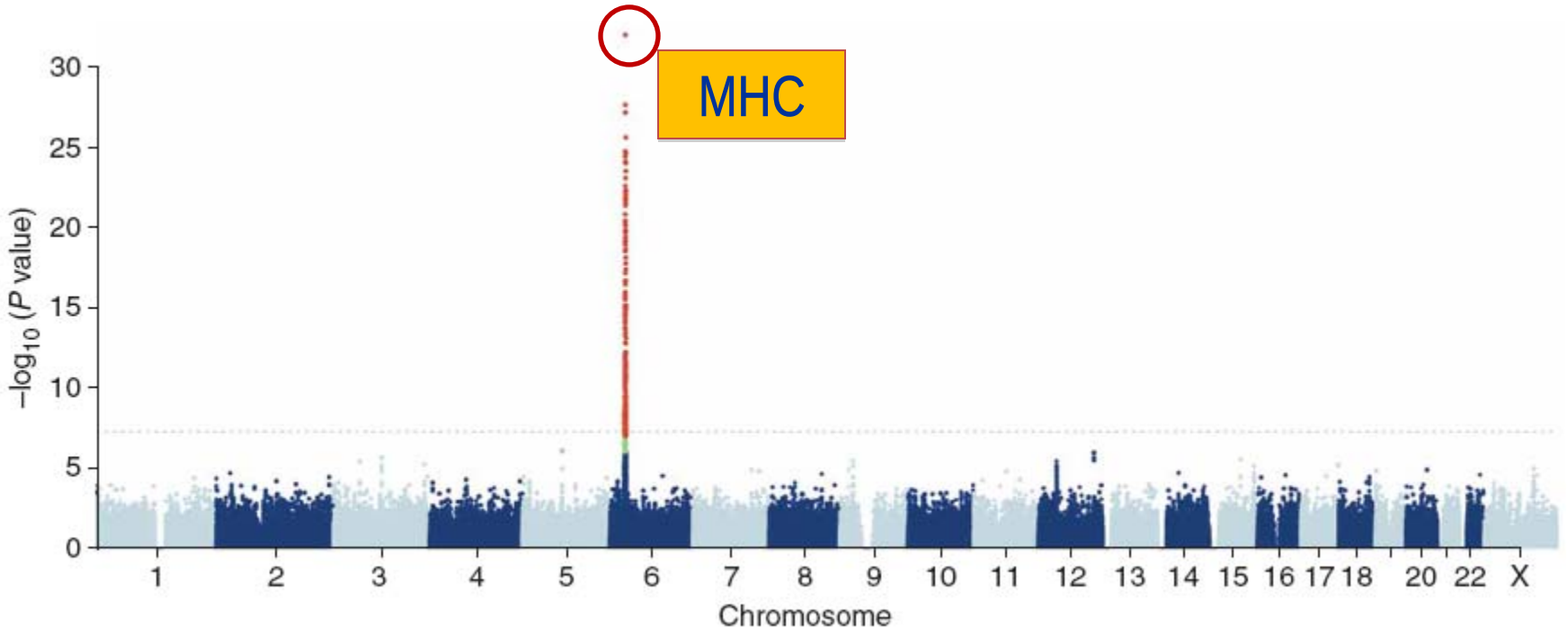
- Matching phenotyped cases and controls for pharmacogenetic research on important drug-induced SAEs: TdP, Liver toxicity, Allergic Reactions
- Developing effective whole genome genotyping and sequencing methods for SAE research
- Supporting the development of the computational methods necessary for effective GWAS analysis (both genotyping and sequencing)
- Creating a timely and publicly available scientific “databank”(raw data and genetic markers) associated with key drug-induced SAEs
- Managing the intellectual property related to genetic markers associated with SAEs, to ensure broad and open access to all users in all settings
- Initiated in concert with FDA as part of Critical Path Initiative

International Serious Adverse Event Consortium (iAES)

nature genetics

*HLA-B*5701* genotype is a major determinant of drug-induced liver injury due to flucloxacillin

Ann K Daly[1], Peter T Donaldson[1], Pallav Bhatnagar[1], Yufeng Shen[2], Itsik Pe'er[2], Aris Floratos[2], Mark J Daly[3], David B Goldstein[4], Sally John[5], Matthew R Nelson[6], Julia Graham[1], B Kevin Park[7], John F Dillon[8], William Bernal[9], Heather J Cordell[1], Munir Pirmohamed[7], Guruprasad P Aithal[10,11] & Christopher P Day[1,11], for the DILIGEN study[12] and International SAE Consortium[12]



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Regulatory Science Activities: Internal Processes

VXDS

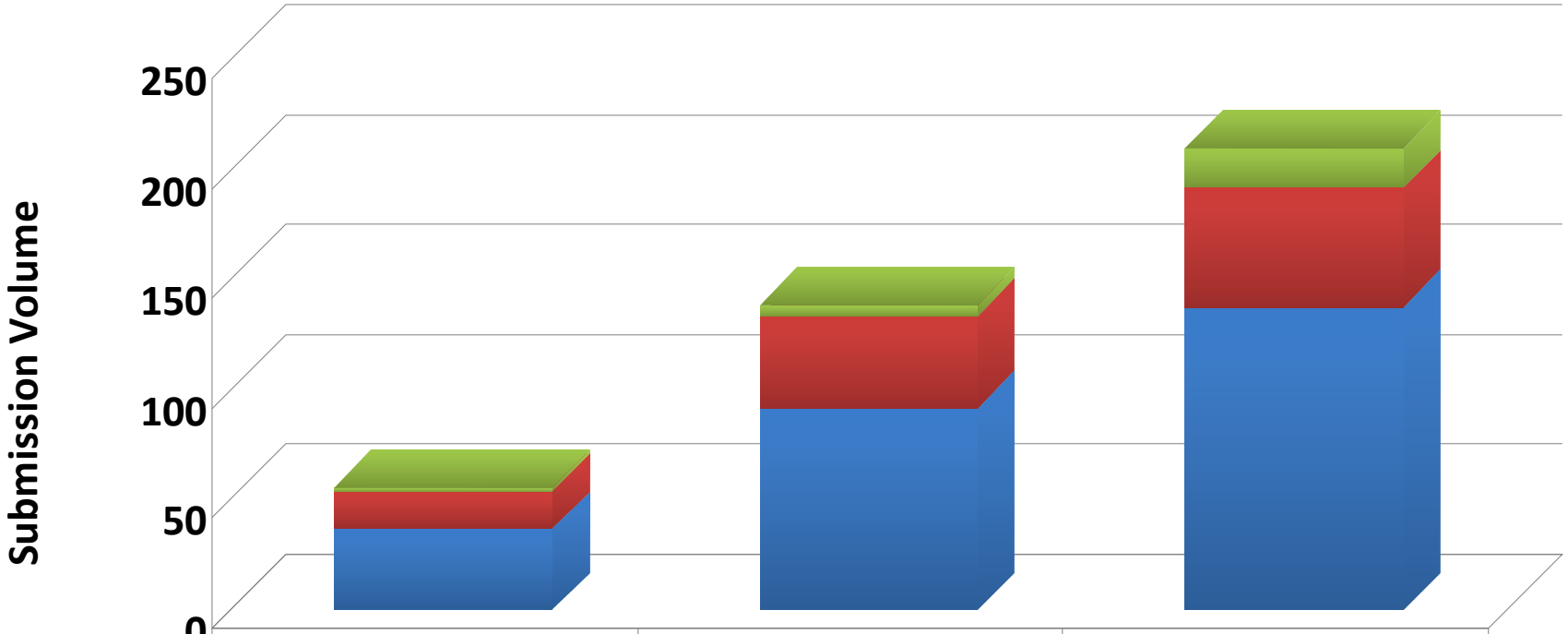
Development of a Semi-Quantitative Risk-Benefit Tool to be used by reviewers

Supporting Regulatory Innovation Via Internal Process Improvement

Voluntary ‘x-mic’ Data Submissions (VXDS)

- Much ‘omic data are of an exploratory or research nature and not yet ready for an IND, NDA or BLA.
- FDA Staff and industry need a ‘non-regulatory’ means of discussing this new science before a submission
  - Helps to ensure regulatory scientists are familiar with and prepared to appropriately evaluate future genomic submissions
- FDA set up new meetings (VXDSs) to share information with the FDA in a protected non-regulatory space
  - Any question can be asked
  - Answers not binding on the FDA

CDER OCP Genomics Group Review Activity: 2008 - 2010



	2008	2009	2010
BLA	2	5	18
NDA	17	42	54
IND	37	92	138

Calendar years; NDAs and BLAs include supplements

Supporting Regulatory Innovation Via Internal Process Improvement

Development of Standardized Benefit-Risk Grid and assessment process for FDA reviewers

- FDA benefit risk (B-R) assessment has been rigorous but informal
- A defined B-R process can aide communications about how decisions were made and the nature of the benefits and risks for a drug
- A defined B-R process can improve communications between Divisions in FDA
  - Assure that all of the available data are considered in the B-R calculation

Desirable Properties of a B-R Framework

- Simple and user-friendly
- Address critical issues
- Capture expert views faithfully
- Represent transparently
- Compatible with quantitative analysis of clinical benefit and safety information
- Facilitate communications (internal and external)
- Broadly applicable

Initial Case Study Work

- CDER explored several past regulatory decisions with the following objectives:
  - Capture the key factors considered in decision-making
  - Using these cases, develop an analytical framework that could serve as a template for the full range of FDA's B-R decisions
  - Ensure that the framework also has potential for communicating benefit-risk decisions to internal and external audiences
  - Now Applying this to new applications

Key Considerations in Drug Regulatory Decision-Making

- Key considerations that influence decision-making:
  - Severity of Condition
  - Unmet Medical Need
  - Clinical Benefit
  - Risk
  - Risk Management

Potential Benefit-Risk Framework Being Rolled Out

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Severity of Condition		
Unmet Medical Need		
Clinical Benefit		
Risk		
Risk Management		

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

---Alfred North Whitehead

Summary/Conclusions

- This is a transformational time in the healthcare system. Expectations, resources, and challenges all changing.
- Clear role for the regulator in supporting needed changes:
  - Communication
  - Collaboration
  - Internal Process Improvement
  - Willingness to question assumptions