New Paradigms in Drug Discovery: Partnerships in Genomics- and Biomarker-Enabled Drug Development, Approval and Prescribing

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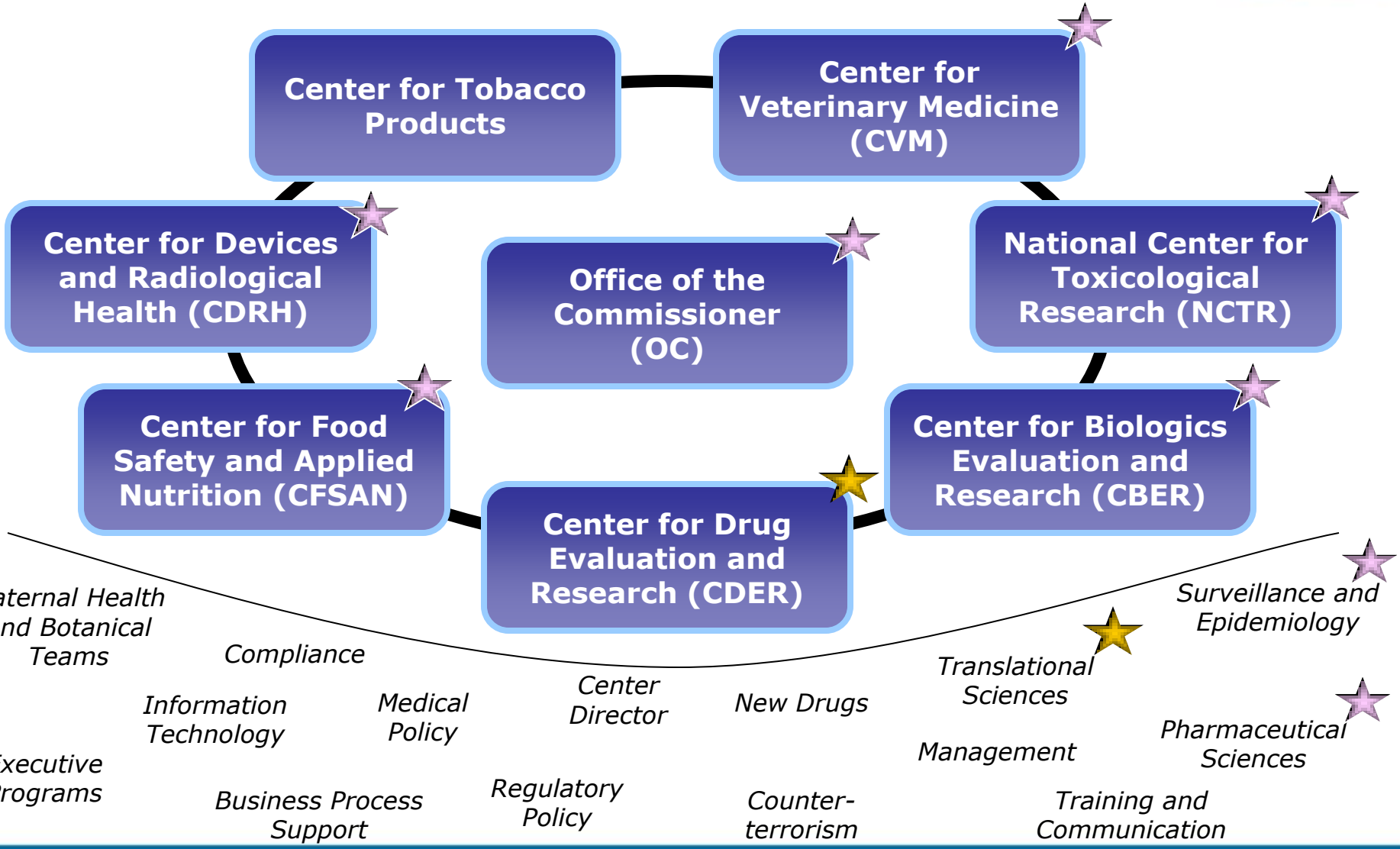
Charge

- How does regulatory policy influence the use and utility of genomics-based drug development?
- What have been the effects of the Voluntary Exploratory Data Submissions (VXDS) Program? What would improve that program?
- What are the incentives for entering into partnerships…strengths, weaknesses and challenges?
- How does genomic information give strength and leverage to partnerships? What is unique about genomics than can accelerate a paradigm change?

The FDA Genomics/ Personalized Medicine Universe



At Odds

- FDA mandate: protect and promote public health
- Tension between *protection* and *promotion*, *risk aversion* and *innovation*, *regulation* and *flexibility*

- However -

- Personalized medicine is challenging our habits of reasoning
- FDA has (arguably) been on the leading edge

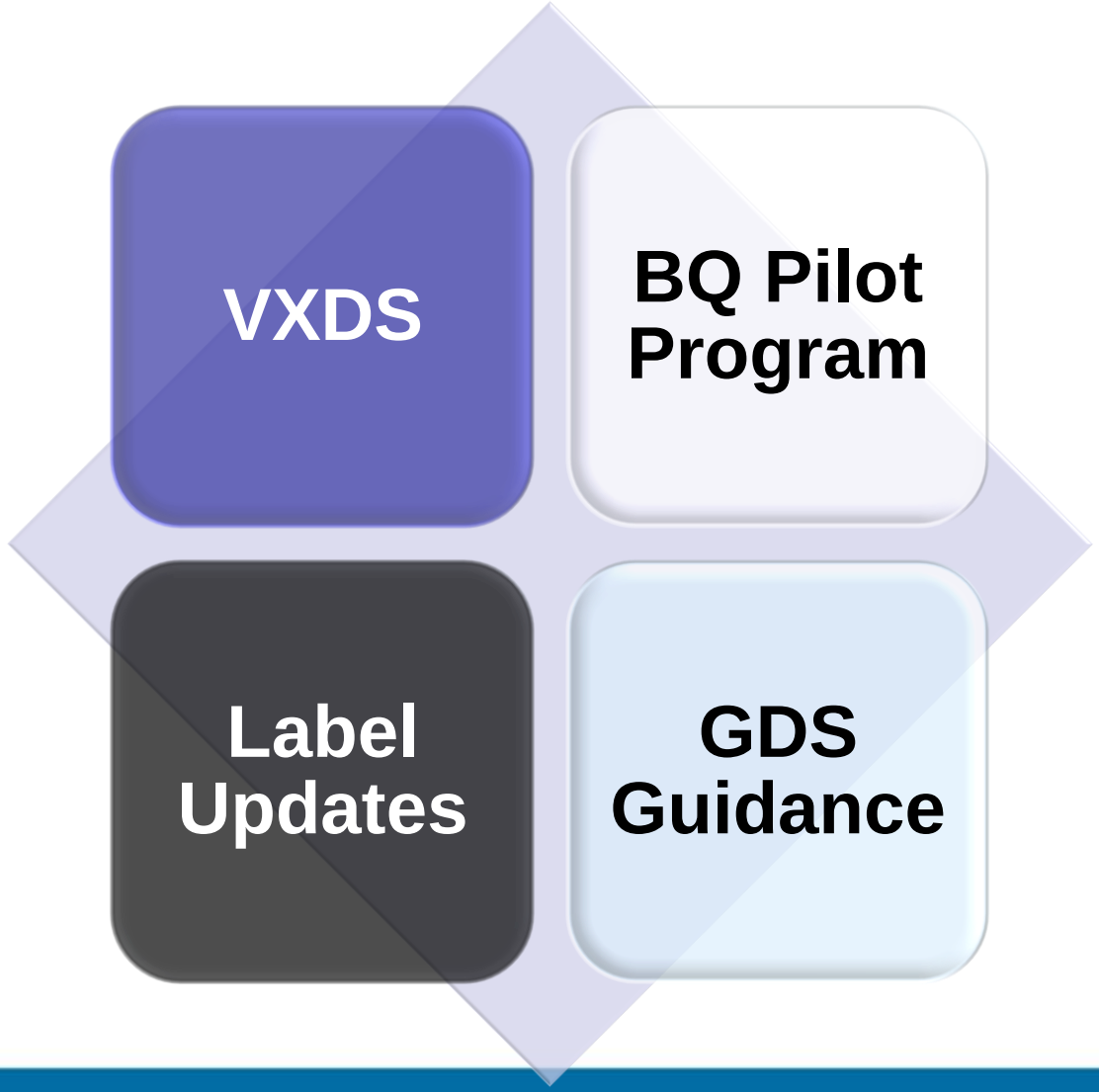
Application of metabolic data to the evaluation of drugs.

A report prepared by the committee on problems of drug safety of the drug research board, National Academy of Sciences-National Research Council

C. 1970

"It is no longer possible to prescribe drugs rationally on the basis of a memorized schedule of dosages and contraindications since the same dose administered to different individuals or the same individual at different times may achieve a therapeutic, a toxic, or an inadequate effect."

Innovation at CDER: Early Focus Areas and Programs



Benefits of VXDS

- Share data informally without regulatory consequences
- Obtain feedback on trial designs, methodologies, data interpretation
- Gain insight into evolving regulatory processes
- Provide experience to facilitate policy development
- Discuss data elements to streamline NDA/BLA submission
- Educate FDA scientists on emerging data and innovative approaches
- Potential for synergizing with scientists from academic, diagnostic, pharma, biotech, PBM, and other settings

See Goodsaid, et al. NRDD 2011 for additional information

VXDS → NDA/BLA
NME Clinical PGx Issues – 2011

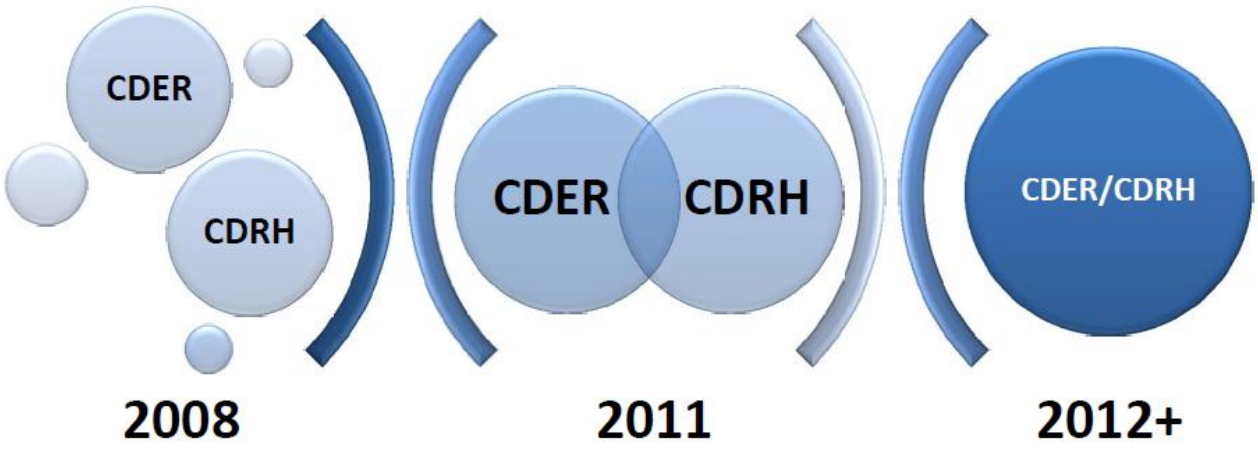
Drug	Approval	Issues
Ruxolitinib	11/16	Efficacy/safety by JAK2 variant status
Clobazam	10/24	Dosing for CYP2C19 status
Crizotinib	8/26	Co-developed (ALK status)
Ticagrelor	7/20	PD and efficacy by CYP2C19 status
Indacaterol	7/1	PK by UGT1A1 status
Belatacept	6/15	Safety by EBV/CMV status
Ezogabine	6/10	PK by UGT1A1 and NAT2 status
Telaprevir	5/23	Efficacy by IL28B, safety by HLA
Boceprevir	5/13	Efficacy by IL28B, safety by ITPA
Ipilimumab	3/25	PGx of safety
Belimumab	3/9	Efficacy by SLE biomarkers
Roflumilast	2/28	Safety potential by human vs. animal genome
Vliazodone	1/21	PGx of efficacy and safety
Vemurafanib	8/17	Co-developed (BRAF status)

Have We Arrived?

CAPSULES
XALKORI®
CRIZOTINIB

ZELBORAF™
(vemurafenib) tablets

kalydeco™
(ivacaftor) tablets

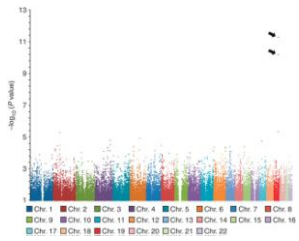


Regulatory Guidance

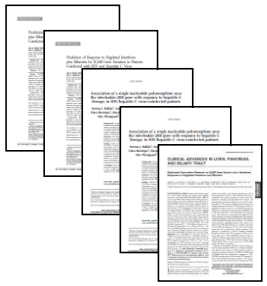
2005	Guidance on PG Data Submissions
	Concept Paper on Drug-Diagnostic Co-Development
2007	Companion Guidance on PG Data Submissions
	Guidance on PG Tests and Genetic Tests for Heritable Markers
2010	ICH E16 Concept Paper on PG Biomarker Qualification: Format and Data Standards
	Guidance on Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Agents for Treatment
	Guidance on Qualification Process for Drug Development Tools
2011	Guidance on Clinical PG: Premarketing Evaluation in Early Phase Clinical Studies
	Guidance on in vitro Companion Diagnostic Devices
In Process	Guidance on Clinical Trial Designs Employing Enrichment Designs to Support Approval of Human Drugs and Biological Products

Paradigm Change and the 'Progressive Reduction of Uncertainty'

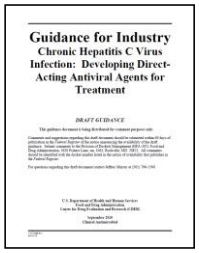
- Attrition not necessarily amenable to changes in regulatory environment
- Advantage of personalized medicine development is not less data, but rather a higher probability of success; shift to "quick win, fast fail"
- Regulatory policy has attempted to foster use of applied genomics in drug development



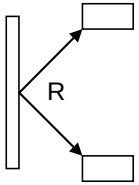
GWAS IL28B predicts Peg-IFN/RBV response



Dozens replicate



FDA HepC guidance



Standard analysis in RCTs

New NDAs

Partnerships

- Domains
  - Effectively develop qualified tools, surrogate biomarkers
  - Create drug safety research infrastructure
  - Comparative effectiveness
- Selected FDA partnerships
  - Consortia: C-Path PSTC, SAEC, BC
  - Academia: CERSI, CSRC
  - Government: CMS, VA, DoD, AHRQ, NIH
  - HMOs, payers: Kaiser Permanente, HealthCore
- Is precompetitive collaboration an elusive goal?

Genomic Science Agenda

- **FDA Priorities**
  - Stimulate innovation in…personalized medicine
  - Ensure FDA readiness to evaluate emerging technologies
  - Harness data through information sciences
- **CDER Needs**
  - Access to post-market data sources
  - Improve risk assessment/management strategies
  - Develop predictive models of safety and efficacy
  - Improve clinical trial design, analysis, and conduct
  - Enhance individualization of patient treatment
- **PDUFA Enhancements**
  - Expand Agency biomarker and PGx teams

Summary

- FDA is committed to personalizing medicine and individualizing therapeutics
- PGx characterization part and parcel to sound drug development, Rx/Dx co-development on the rise
- Improved industry guidance and inter-center/agency communication will promote genomic applications in drug development
- Clinical implementation of genomic technologies is and will continue to be complex (cultural, logistical, informatic), partnerships necessary