Drug Interactions with Hormonal Contraceptives:
Public Health and Drug Development Implications

Regulatory Science and Research Opportunities in Evaluation of Drug Interactions with Hormonal Contraceptives

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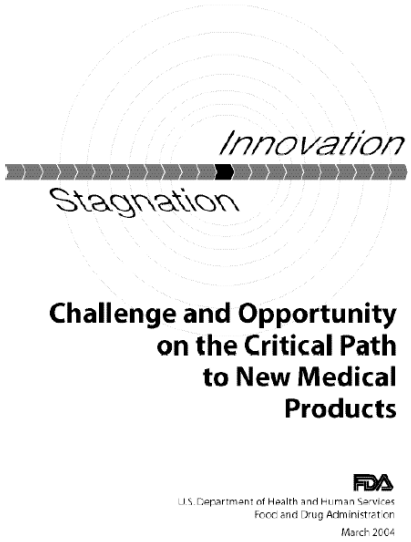
Disclaimer

- The opinions expressed in this presentation are mine and do not necessarily reflect the official views of the U.S. Food and Drug Administration (FDA).

FDA's Strategy for Driving Innovation

Critical Path Initiative



2004 & 2006

Strategic Plan for Regulatory Science

Regulatory science:
"…the science of developing new tools, standards and approaches to assess the safety, efficacy, quality and performance of FDA-regulated products."

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
U.S. FOOD AND DRUG ADMINISTRATION

2011

CDER Scientific and Research Needs Document

July | 11

Identifying CDER's Science and Research Needs Report

July 2011

The CDER Science Prioritization and Review Committee (SPaRC)

Center for Drug Evaluation and Research

July 2011

http://www.fda.gov/downloads/Drugs/ScienceResearch/UCM264594.pdf

Seven Major Categories

1. Improve Access to Post-market Data Sources and Explore Feasibility of Their Use in Different Types of Analyses
2. Improve Risk Assessment and Management Strategies to Reinforce the Safe Use of Drugs
3. Evaluate the Effectiveness and Impact of Different Types of Regulatory Communications to the Public and other Stakeholders
4. Evaluate the Link Among Product Quality Attributes, Manufacturing Processes, and Product Performance
5. Develop and Improve Predictive Models of Safety and Efficacy in Humans
6. Improve Clinical Trial Design, Analysis, and Conduct
7. Enhance Individualization of Patient Treatment

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Key regulatory questions and knowledge gaps regarding drug interactions with hormonal contraceptives

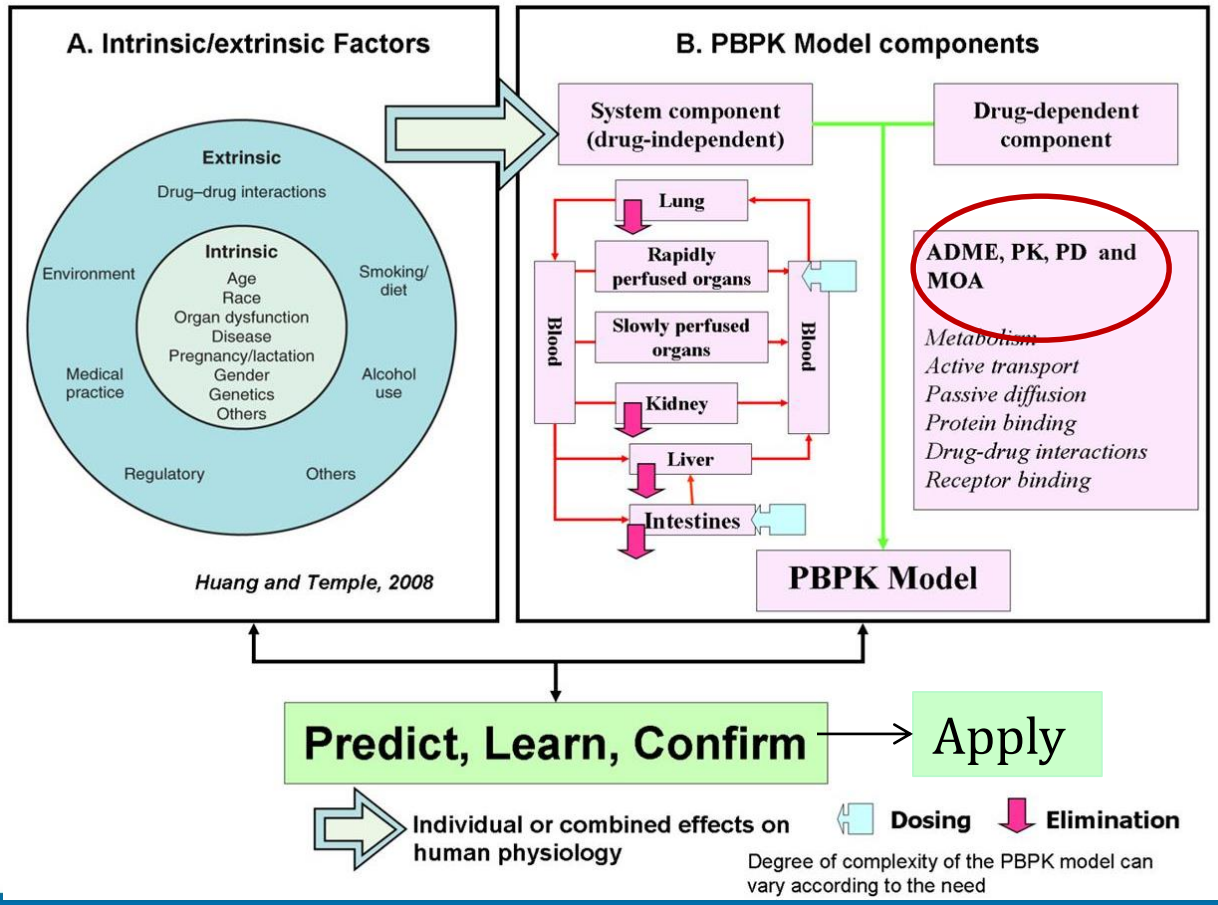
- Key considerations for study design
  - How to maximize knowledge gained for decision-making
- Data translation and extrapolation
  - Need to understand metabolic/transport pathways
  - Need to understand exposure-response
- Labeling and health communication
- Therapeutic areas that warrant more research to understand HC use

Research Needs and Tools

One tool for DDI Prediction

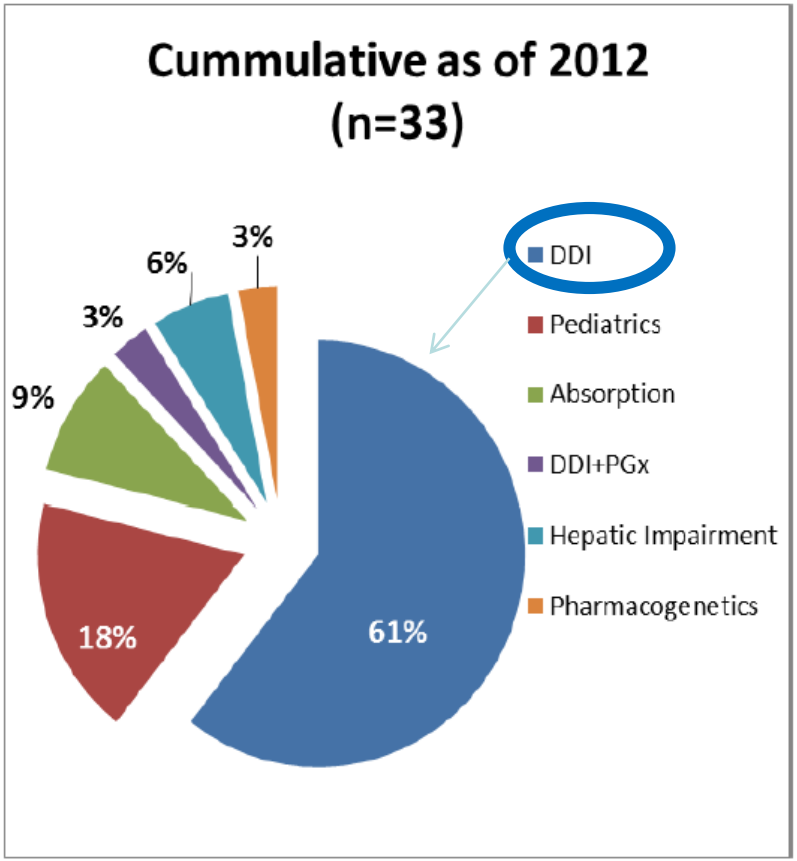
Applications of Physiologically Based Pharmacokinetic (PBPK) Modeling and Simulation During Regulatory Review

P Zhao[1], L Zhang[1], JA Grillo[1], Q Liu[1], JM Bullock[1], YJ Moon[1], P Song[1], SS Brar[1], R Madabushi[1], TC Wu[1], BP Booth[1], NA Rahman[1], KS Reynolds[1], E Gil Berglund[2], LJ Lesko[1] and S-M Huang[1]

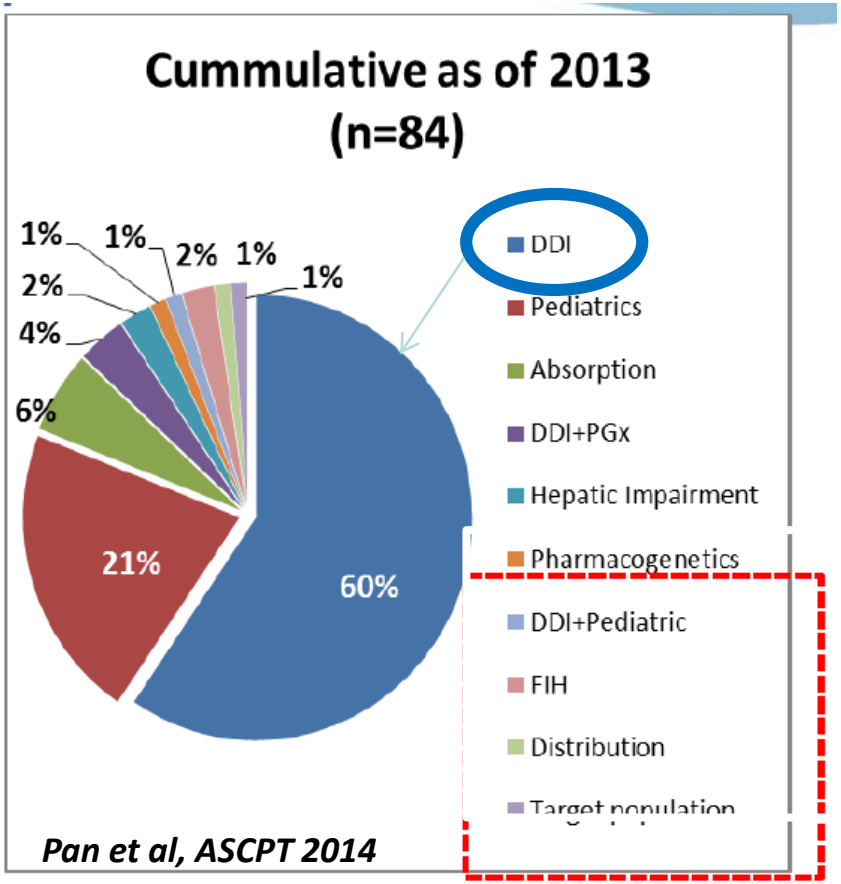


Clin Pharmacol Ther, 2011

Regulatory Submissions with PBPK Data



Huang et al, J Pharm Sci, 2013

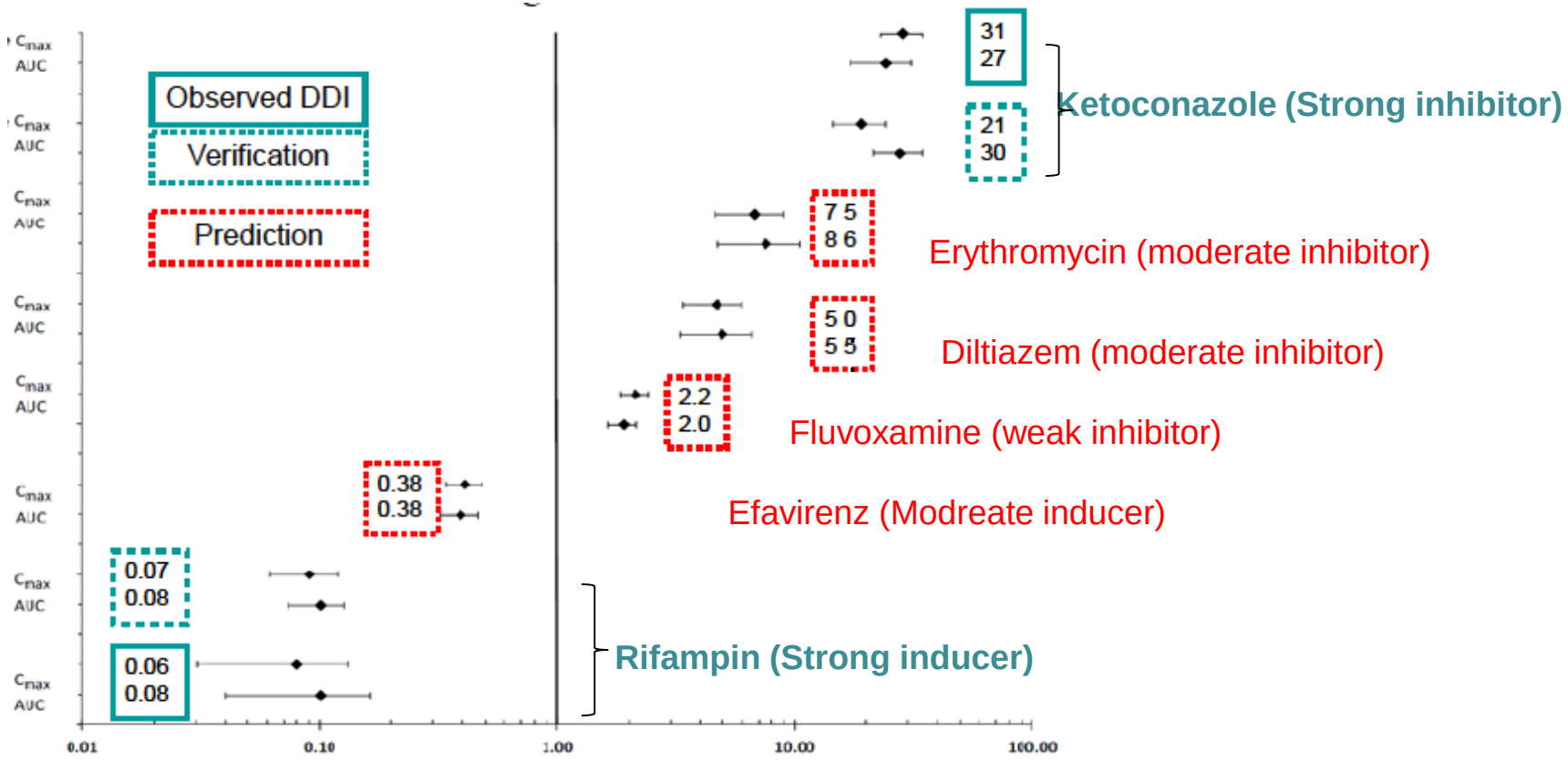


Pan et al, ASCPT 2014

- **Increased use of PBPK by drug developers**
- **Majority of the cases were related to DDI (~60%)**

PBPK & Drug Interactions Example: Ibrutinib

PBPK-Simulated and observed Cmax and AUC ratios (mean and 95% confidence interval)



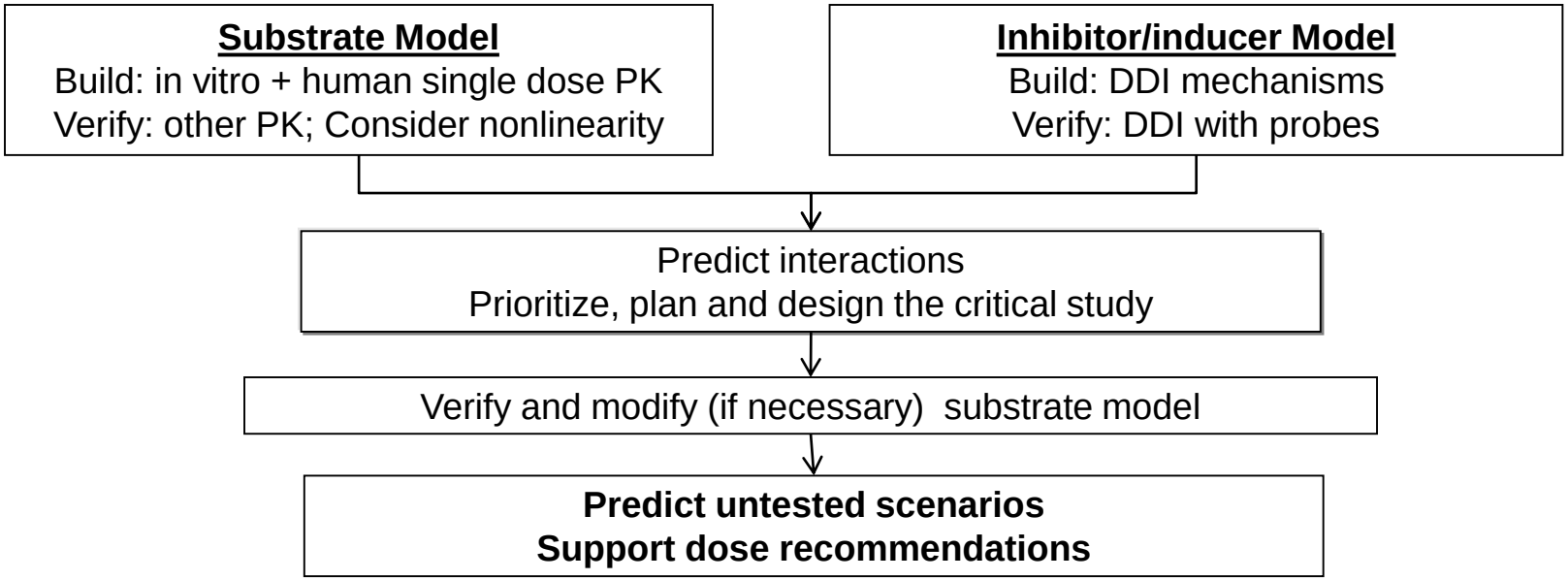
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/205552Orig1s000ClinPharmR.pdf

Using PBPK to Predict CYP-Mediated DDI

- Sufficient dataset to demonstrate predictive performance

[Prerequisites: substrate model predicts base PK; modulator models are verified]

- Together support a generalized WORKFLOW* of using PBPK:

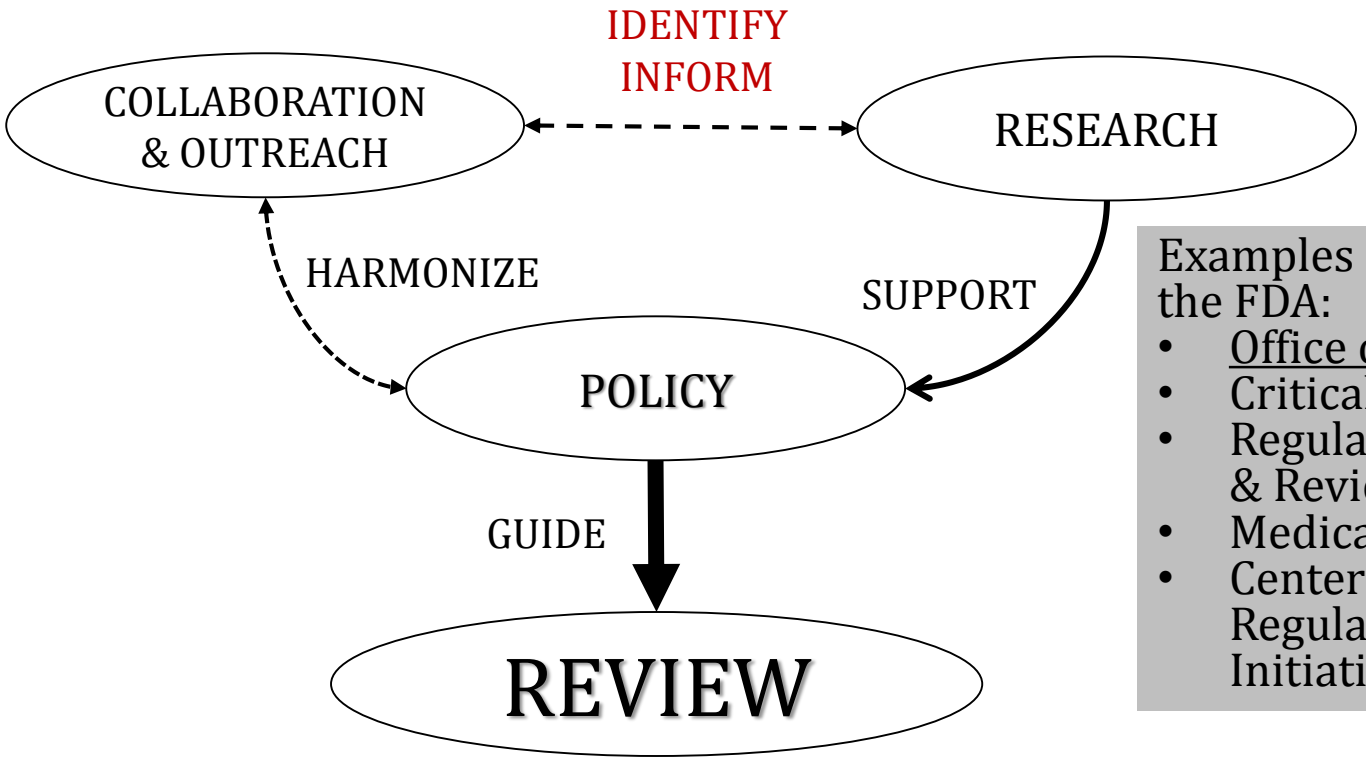


Core message of the three publications:

MdLT Viera, Pharmacol Ther, 2014 *Wagner, Clin Pharmacokinet 2015* *Wagner, Clin Pharmacokinet Online 2015*

Courtesy: Ping Zhao

Ensure Evidence-based, Consistent, and Quality Review Products to Support Decisions



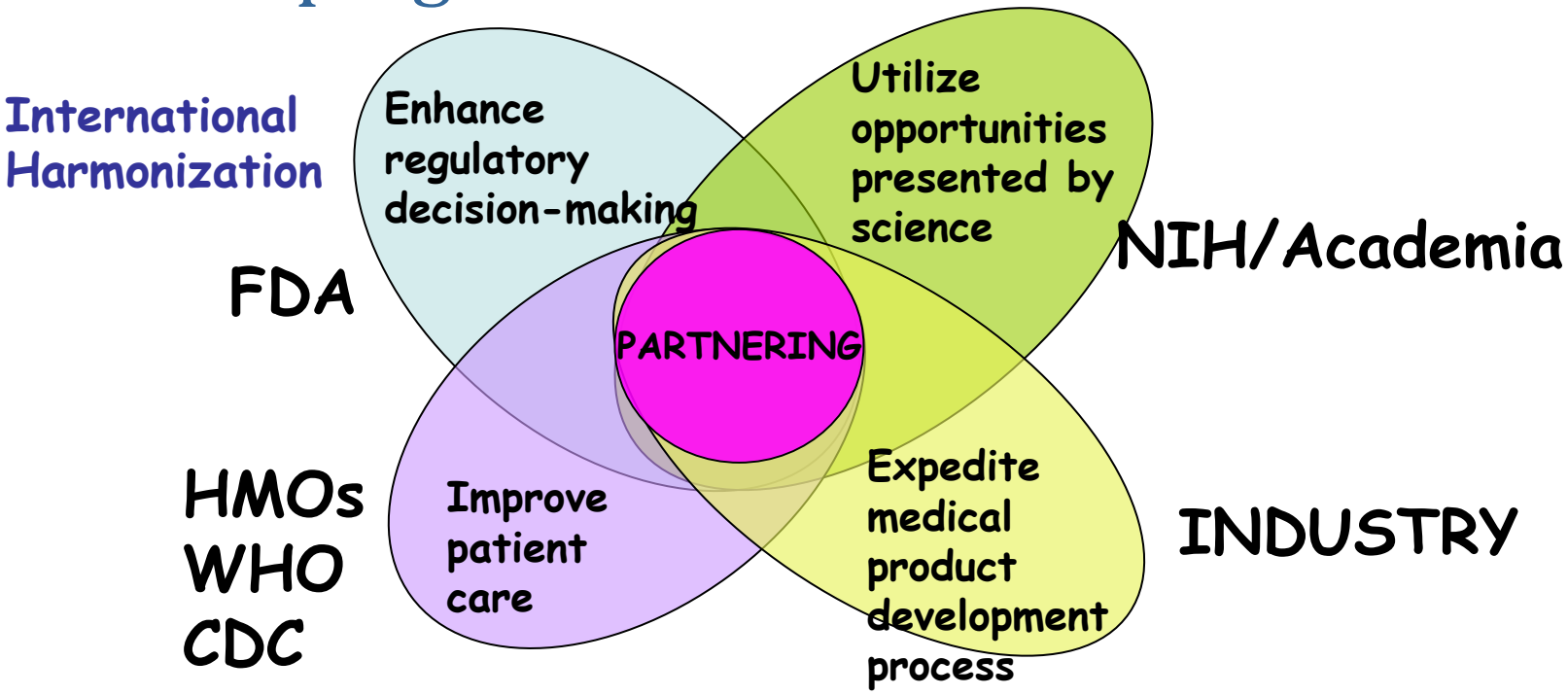
Examples of Research Grants at the FDA:

- Office of Women's Health
- Critical Path
- Regulatory Science Research & Review Enhancement
- Medical Countermeasures
- Center for Excellence in Regulatory Science Initiatives

Courtesy: Ping Zhao

Collaboration is key to future successes

-Work with the larger scientific community on developing solutions



S Buckman, S-M Huang, S Murphy, Clin Pharmacol & Ther, 81(2): 141-144, Feb 2007 (figure 1; adapted from figure supplied courtesy of RM Long, NIH)

Thank you

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