U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

Model Informed Drug Development (MIDD): Opportunities for Collaboration

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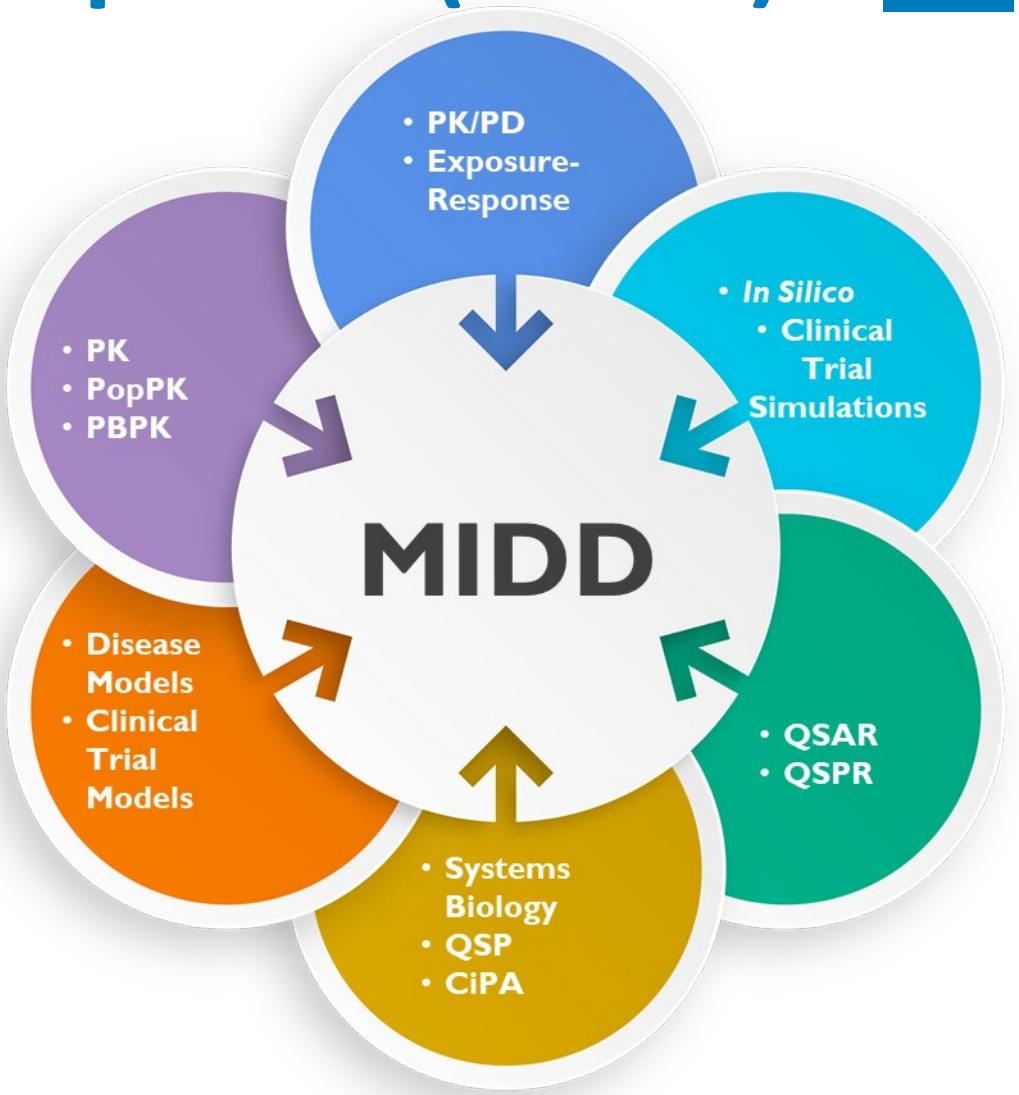
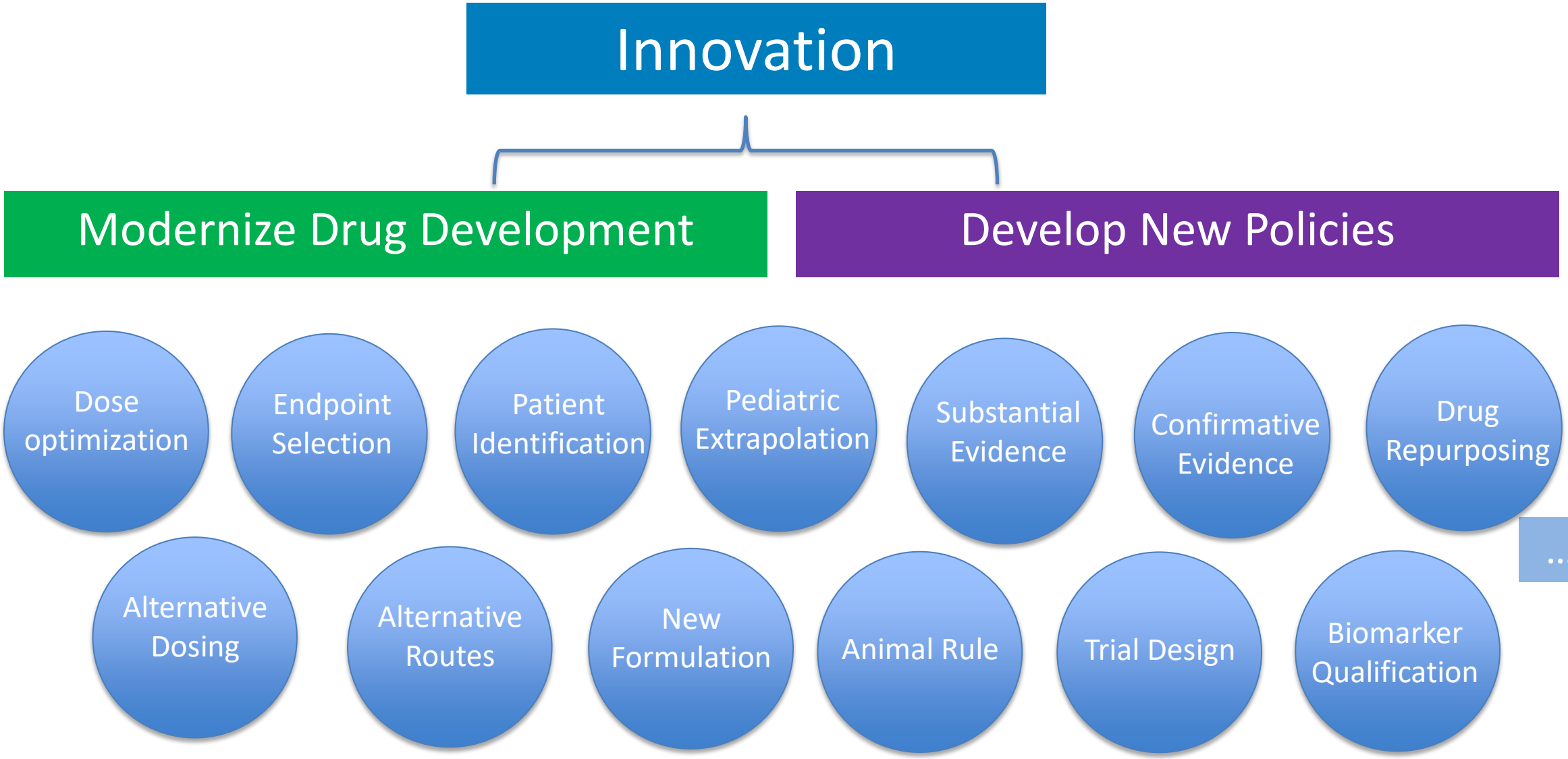
Model-informed Drug Development (MIDD)

Development and application of exposure-based, biological, and statistical models derived from preclinical and clinical data sources to address drug development or regulatory issues*



* From PDUFA 6; Excludes statistical designs involving complex adaptations, Bayesian methods, or other features requiring computer simulations to determine the operating characteristics of a confirmatory clinical trial.

Application of MIDD



MIDD Paired Meeting Program

- This program is jointly administered by CDER and CBER.
- OCP is the point of contact.
- The product should be registered under an U.S. IND/NDA/BLA.
- FDA accepts requests on a continuous basis.
- Joint effort from multi-disciplinary review team members

Regulatory Approvals

- **Ramucirumab**

  Approval of shorter infusion option
- **Sotalol Hydrochloride**

  Approval of a new dosing strategy that reduces the hospital stay from 3 days to 1 day
- **Cetuximab**

  Approval of a dosing regimen with extended inter-dosing interval
- **Valbenazine**

  Approval of a new dose option as part of titration
- **Secukinumab**

  Approval of intravenous route of administration for psoriatic arthritis, ankolysing spondylitis, and non-radiographic axial spondyloarthritis

Ramucirumab: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125477s036lbl.pdf
Sotalol Hydrochloride: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022306s005lblrpl.pdf
Cetuximab: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125084s277s280lbl.pdf
Valbenazine: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/209241s020lbl.pdf
Secukinumab: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/125504s066,761349s004lbl.pdf

Fit for Purpose (FFP) Initiative

- The Fit-for-Purpose (FFP) Initiative provides a pathway for regulatory acceptance of dynamic tools for use in drug development programs.
- A designation of 'fit-for-purpose' (FFP) will be established based on a thorough evaluation of the information provided.

Disease Area	Submitter	Tool	Trial Component
Alzheimer's Disease	The Coalition Against Major Diseases (CAMD)	Disease model: Placebo/ disease progression	Demographic & drop out
Multiple	Janssen Pharmaceuticals & Novartis Pharmaceuticals	Statistical model: MCP-Mod	Dose finding
Multiple	Ying Yuan, PhD The University of Texas, MD Anderson Cancer Center Department of Biostatistics	Statistical model: Bayesian Optimal Interval (BOIN) design	Dose finding
Multiple	Pfizer	Statistical Method: Empirically Based Bayesian Emax Models	Dose finding

Link to the FDA FPP initiative:
<https://www.fda.gov/drugs/development-approval-process-drugs/drug-development-tools-fit-purpose-initiative>

Complex Innovative Trial Design (CID) Meeting Program

- Goal: facilitating and advancing the use of complex adaptive, Bayesian, and other novel clinical trial designs, with emphasis in late-stage drug development
- This paired meeting program offers sponsors whose meeting requests are granted the opportunity for increased interaction with FDA staff to discuss their proposed CID approach.
- Originally established under PDUFA VI. Continued under PDUFA VII.

Link to the FDA CID meeting program:
https://www.fda.gov/drugs/development-resources/complex-innovative-trial-design-meeting-program

Collaborations: Leverage the strengths of 2 disciplines

While both disciplines may work on all aspects, they have particular strengths

Clinical Pharmacology:

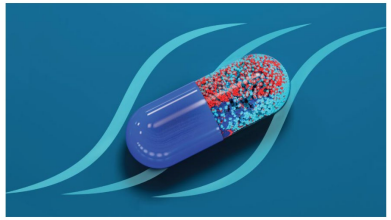
- **Understanding of principles of clinical pharmacology (PK & PD), patient characteristics, and diseases.**
- **Leading to adoption of useful predictions including extrapolation**

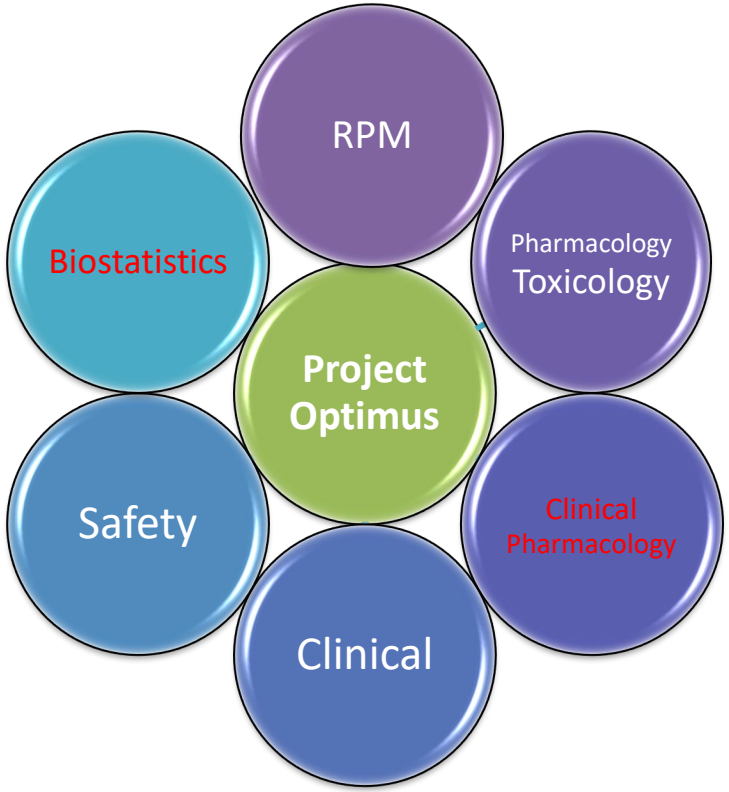
Statistics:

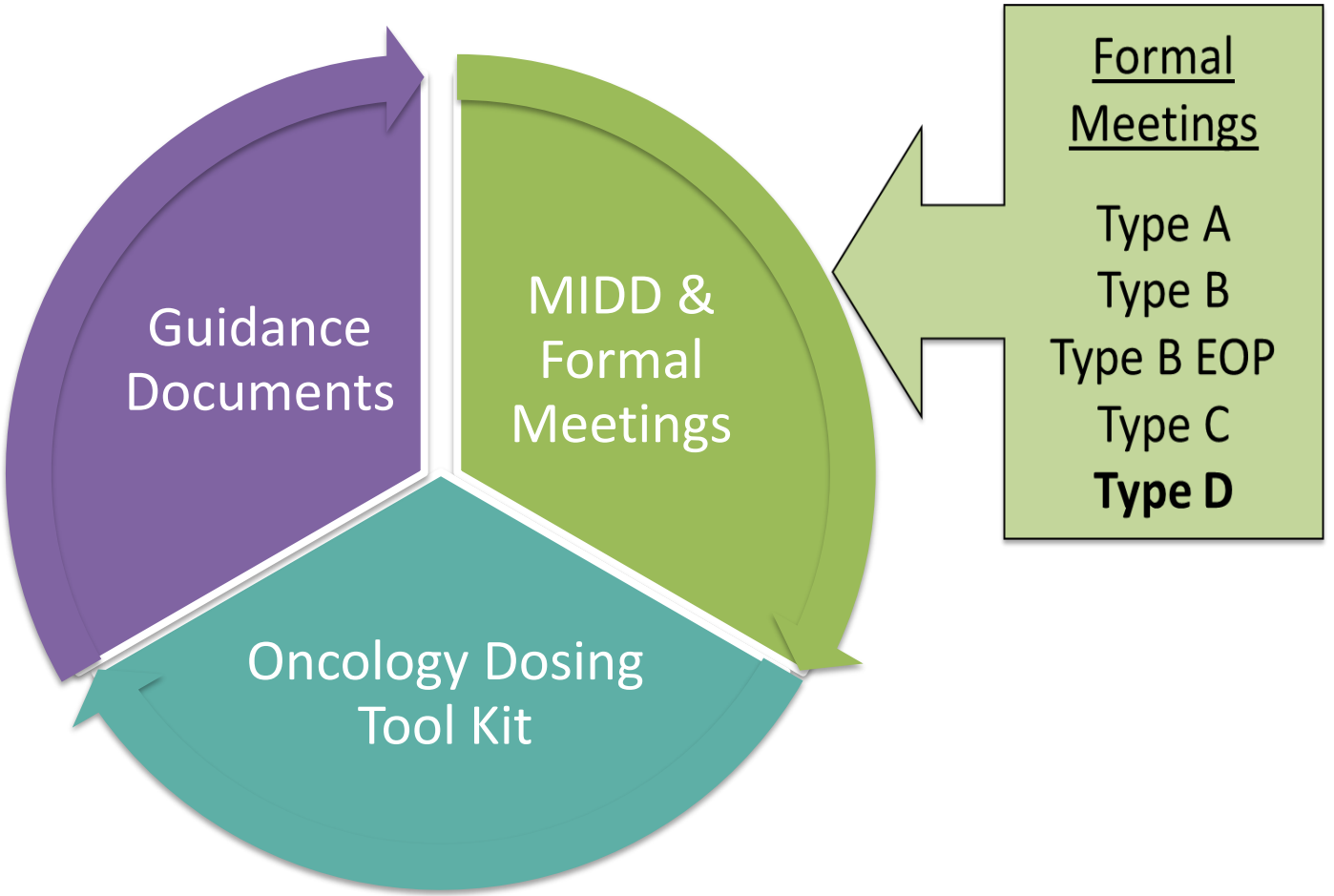
- **Separating exploration vs. confirmatory**
- **Detecting signal vs. noise, sometimes through advanced statistical tools**
- **distinguishing association vs. causation, cautioning interpretation**

Collaborations: design

Project Optimus
to reform the dosage optimization and dose selection paradigm in oncology drug development







Collaborations: modeling

- Adopt useful predictive PK/PD model
- Unleash the power of reasonable extrapolations:
  - from one formulation to another
  - from one population to another
- Plan study including design and analyses
- Model to distinguish data driven noisy/potential signal vs definitive conclusion
- Appropriate interpretation of results and value model validation from independent data

Collaborations: simulation

- Generate data using predictive PK/PD model, incorporating multiple layers of uncertainty:
  - uncertainty in estimating parameter
  - model uncertainty
  - Future data generation uncertainty
- Analyze data through prespecified data-analytical models to make prediction
- Distinguish confidence intervals and predictive intervals

Collaborations: analysis

- Interpret parameters and important measures based on science; diagnose and validate results using empirical experience from similar products/studies
- Different method to quantify variability: large sample asymptotic, exact method, nonparametric method, bootstrap methods, resampling methods, transformation, Bayesian method
- Evaluate model through assessing model stability, model diagnostics and validation

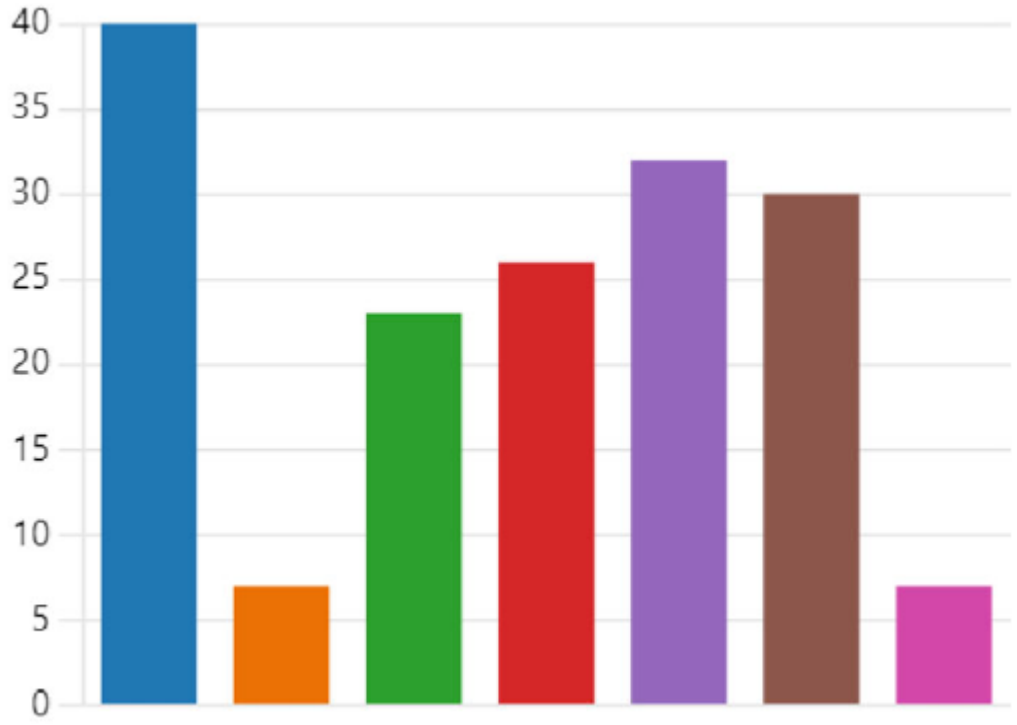
Survey: OB/OCP Collaboration

- 71 Responses
- 37 from OB, 34 from OCP
- 36 reviewers, 38 leadership roles
- Top 3 areas overlapping the most between OB and OCP:
  - NDA/BLA
  - MIDD
  - IND

Survey: OB/OCP Collaboration – Issues of Potential Disagreement

- When scientific disagreement between OB and OCP occurred, what were the overlapping issues or topics that led to the apparent disagreement?

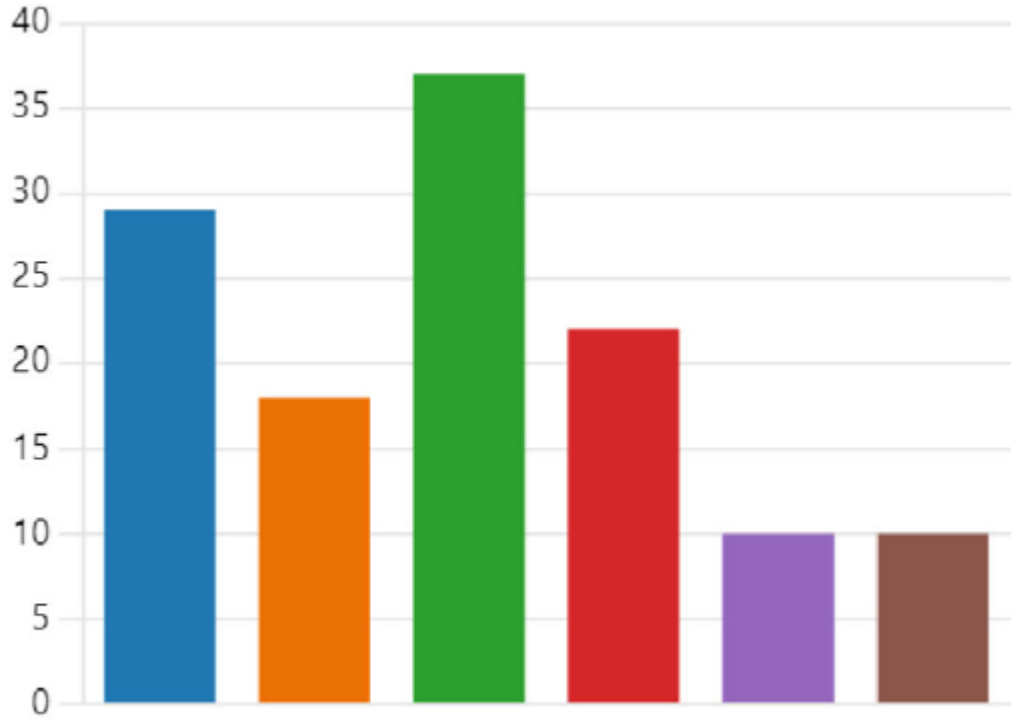
Evidence of effectiveness	40
Safety signal identified	7
Benefit-risk assessment	23
Dose selection rationale	26
Subgroup evaluation	32
Assessment methodology	30
Other	7



Survey: OB/OCP Collaboration – Roadblocks for Agreement

- When scientific disagreement between OB and OCP in regulatory review has occurred, what were the roadblocks in reaching an agreement?

Issue was identified too late	29
Lack of cross-disciplinary experti...	18
Different opinion/experience on...	37
Lack of an effective approach to...	22
Lack of mutual trust	10
Other	10



Occasional Tensions that impede effective collaboration

- Mechanistic vs empirical models
- Adequate model fitting and predictive performance measurement
- Exposure vs doses
- Use of assumption rich models
- Drawing confirmatory conclusions from exploratory analysis
- Inadequate understanding between two

Ease the Tension

- Confirm prediction using independent data
- Lack of confirmatory should not consider as failure but learning opportunity
- Listen, understand, and communication;
- Respect differences, collaboration, and mutual learning
- Public healthy first
- Leadership!

Moving Forward

- MIDD program provides a platform for early interaction among all stake holders to streamline new drug development.
- Collaboration between clinical pharmacologists and statisticians ensures success of the program.
- Joint effort from industry, academia, and regulator is critical to overcome challenges in new drug development and ensure sustainability of the program.

Acknowledgement

OB/OCP working group

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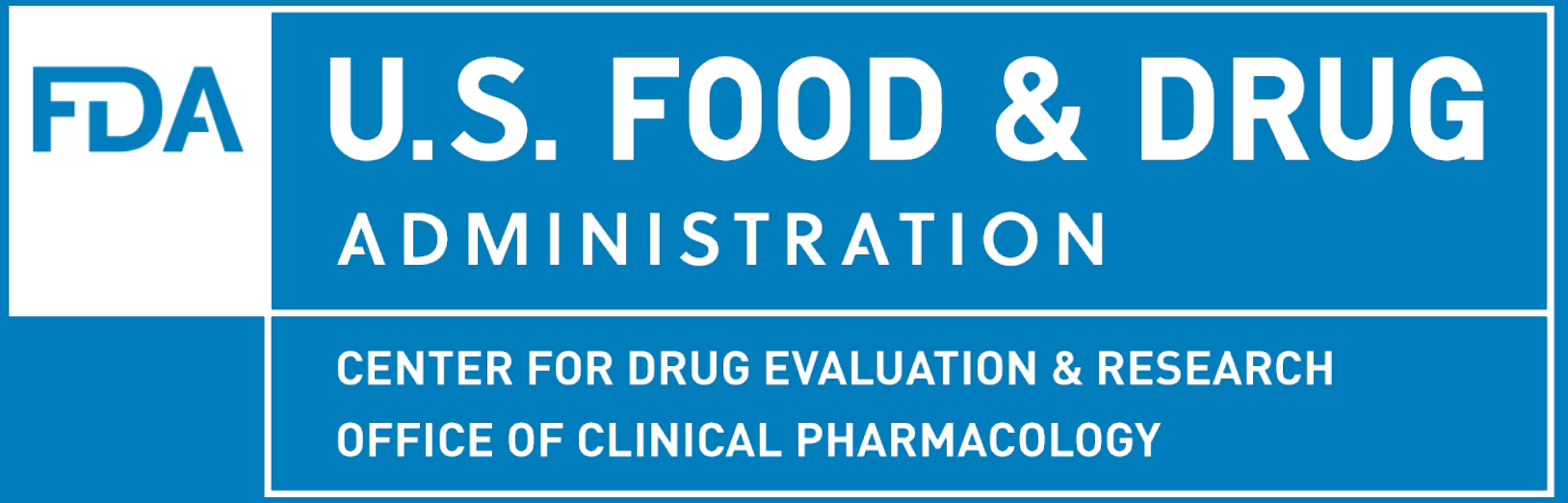
- Dr. Kimberly Bergman
- Dr. Shiew-Mei Huang
- Dr. Issam Zineh
- DPM Members
- OCP Members

Questions and Comments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