# Advancing Model-Informed Drug Development (MIDD) : A Holistic and Integrative Approach

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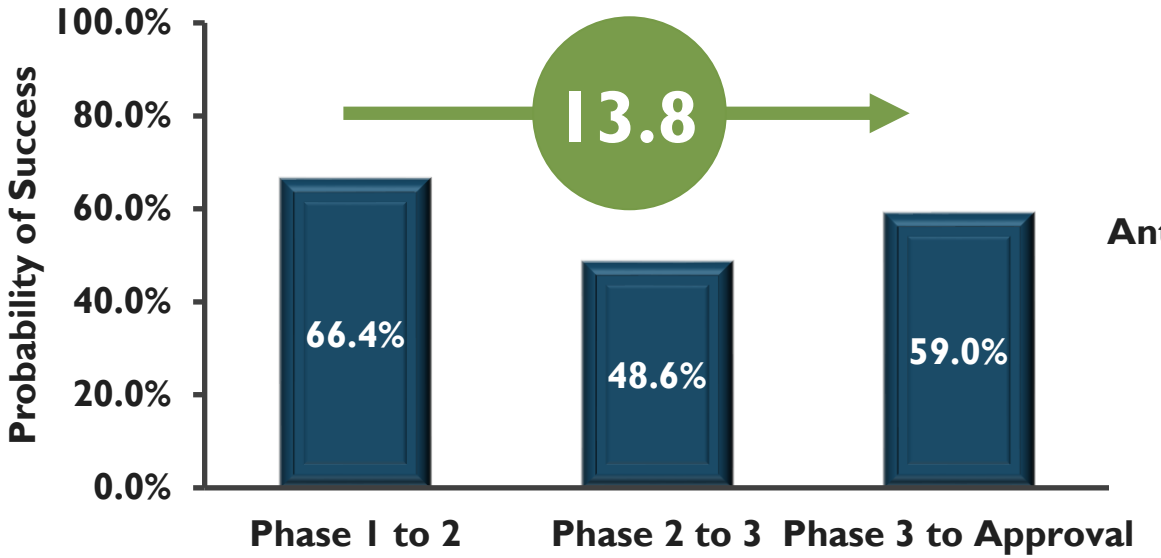
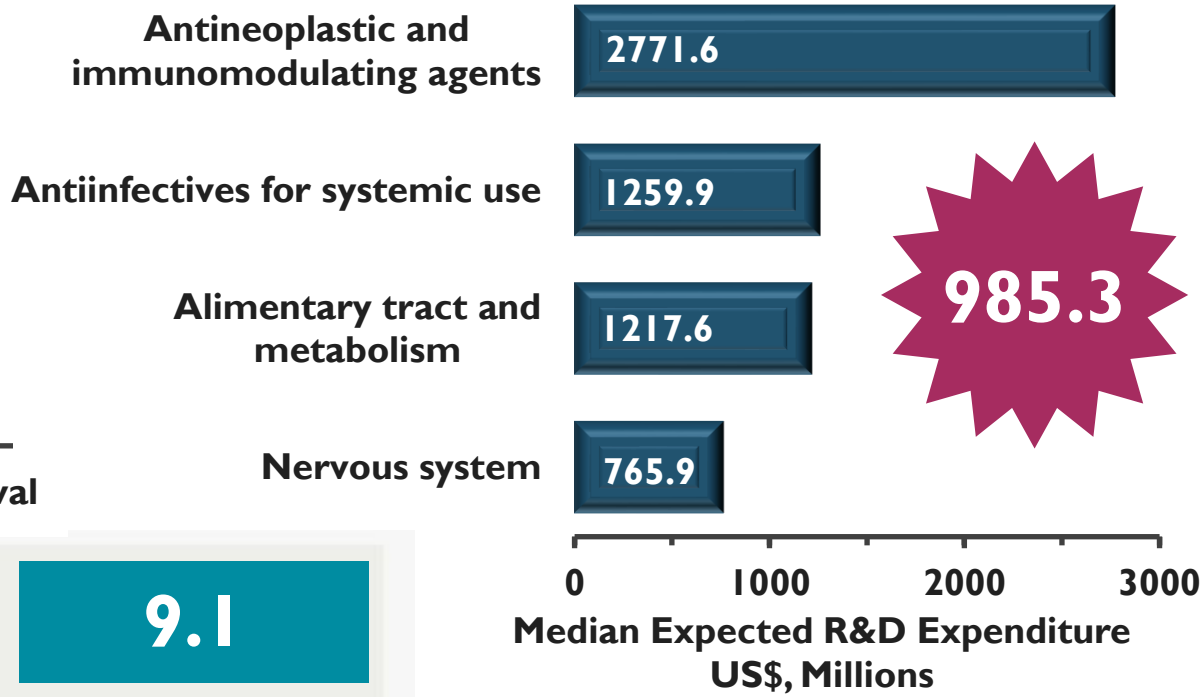
U.S. FOOD & DRUG ADMINISTRATION

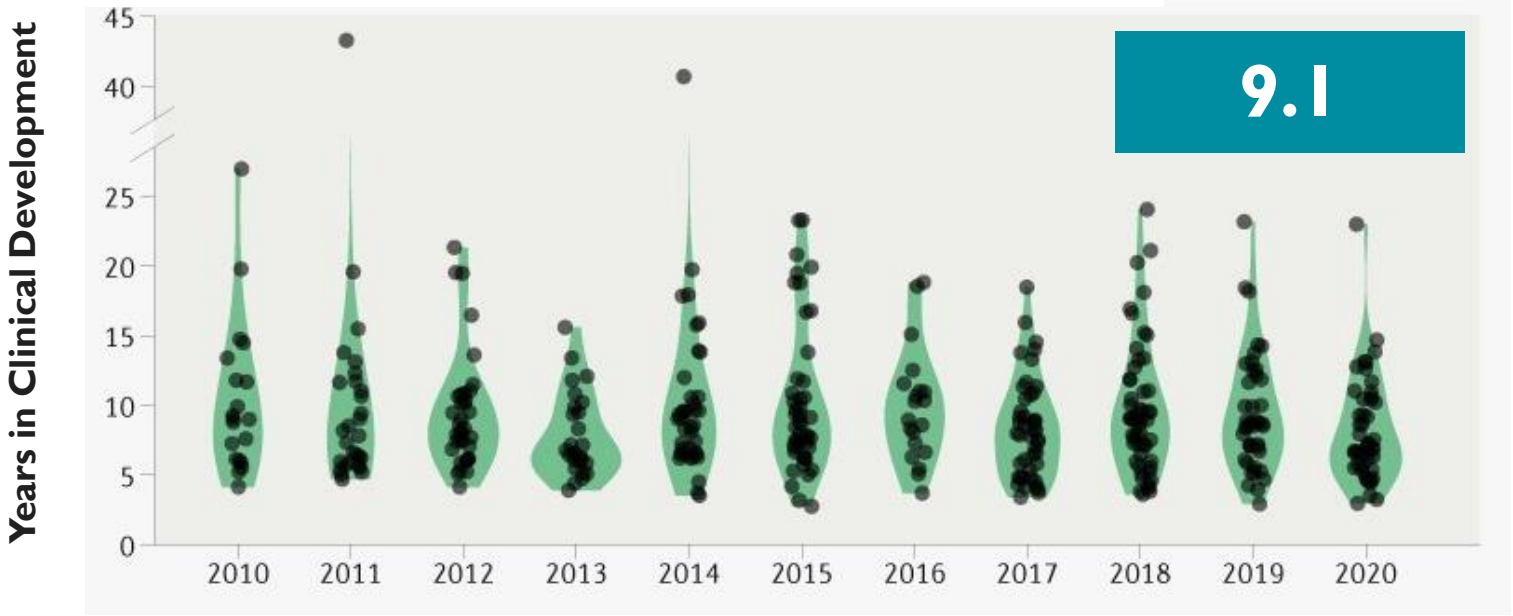
# Disclaimer

**The views and opinions expressed in this presentation represent those of the presenter, and do not necessarily represent an official FDA position.**

# Some Numbers for Context



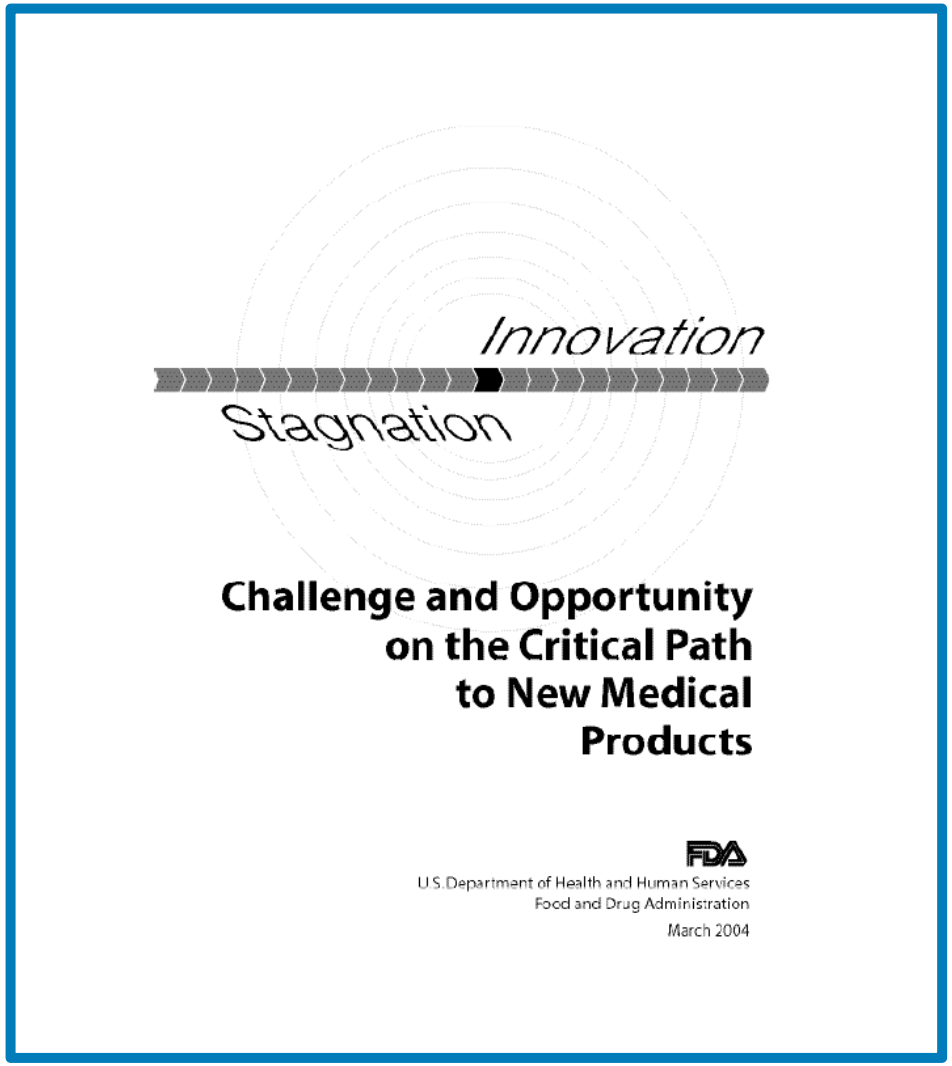


*Wong 2019 [PMID: 29394327]*

*Brown 2021 [PMID: 34759309]*

*Wouters 2020 [PMID: 32125404]*

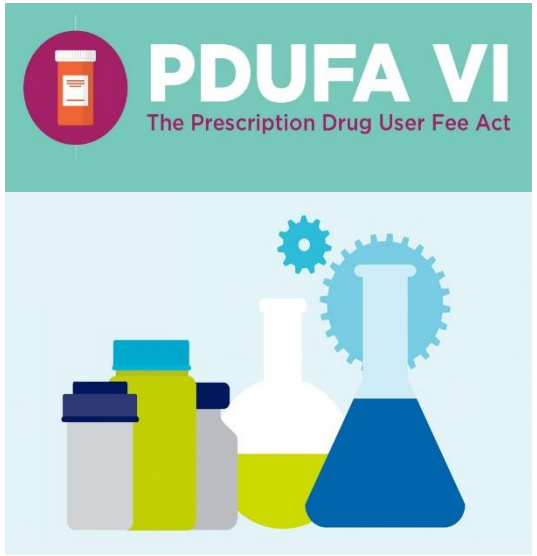
# Negotiating the Critical Path




A new product development toolkit -- containing powerful new scientific and technical methods such as animal or computer-based predictive models, biomarkers for safety and effectiveness, and new clinical evaluation techniques -- is urgently needed to improve predictability and efficiency along the critical path from laboratory concept to commercial product.

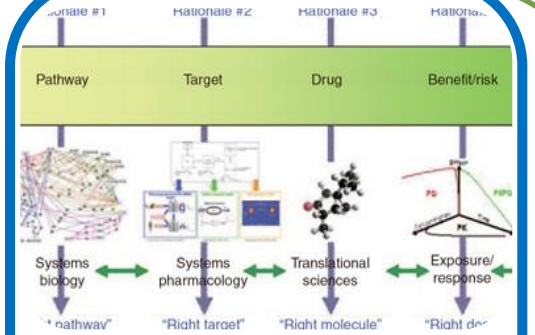
*http://wayback.archive-it.org/7993/20180125035500/https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/UCM113411.pdf*

# PDUFA VI: Regulatory Decision Tools



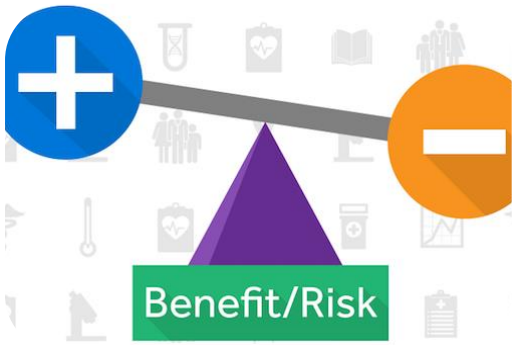

Patient Voice


Complex Innovative Trial Designs




Model-Informed Drug Development

Analysis Data Standards




Benefit/Risk Assessment


Biomarker Qualification

# What is Model-Informed Drug Development?

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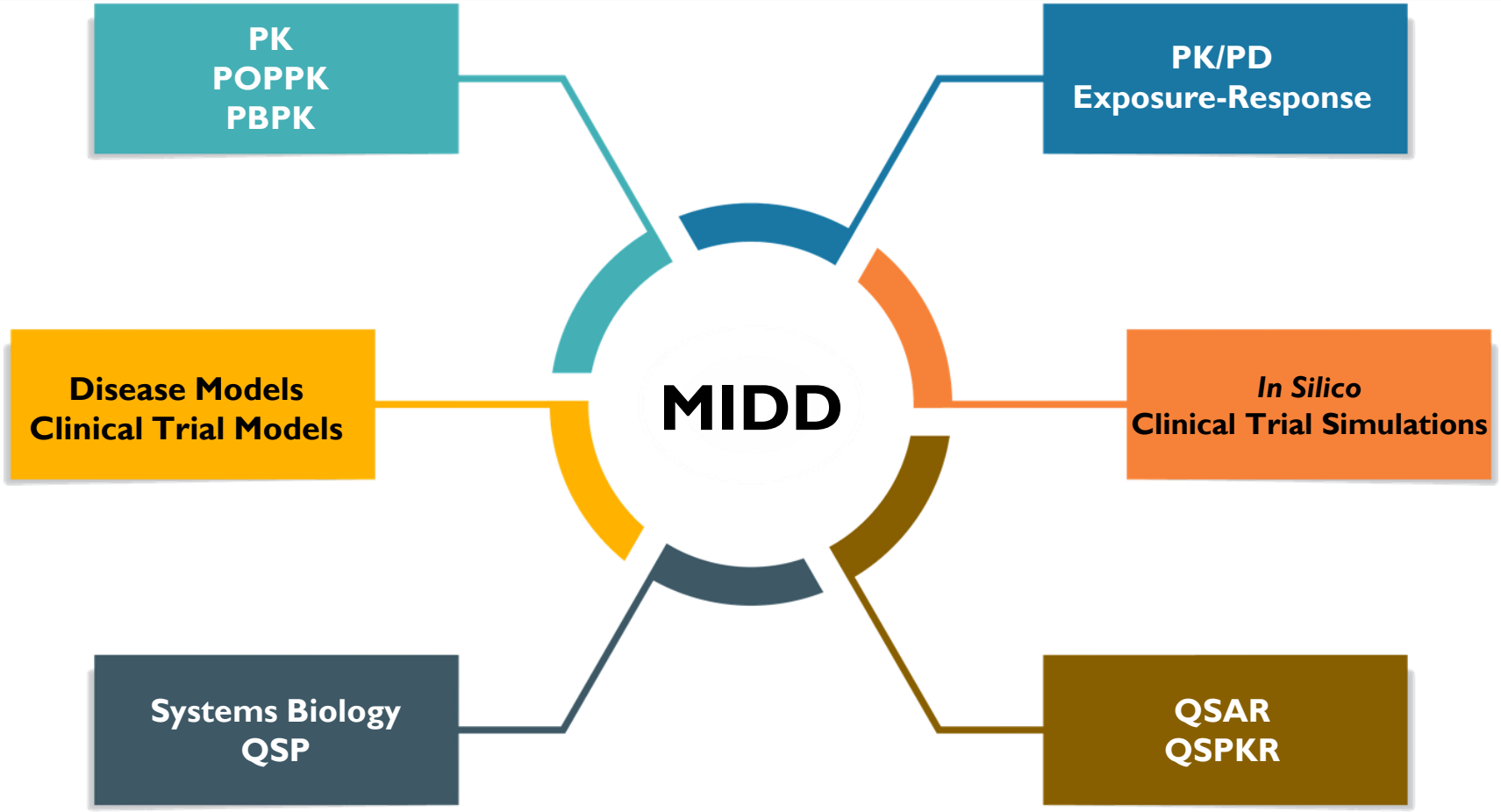
- Development and application of pharmaco-statistical models of drug efficacy and safety from preclinical and clinical data to improve drug development knowledge management and decision-making[1]

- Quantitative framework for prediction and extrapolation, centered on knowledge and inference generated from integrated models of compound-, mechanism-, and disease-level data and aimed at improving the quality, efficiency and cost effectiveness of decision making[2]

- Development and application of exposure-based, biological, and statistical models derived from preclinical and clinical data sources to address drug development or regulatory issues[3]

[1] *Lalonde 2007 [PMID 17522597]* | [2] *Marshall 2016 [PMID 27069774]* | [3] *PDUFA VI Goals Letter*

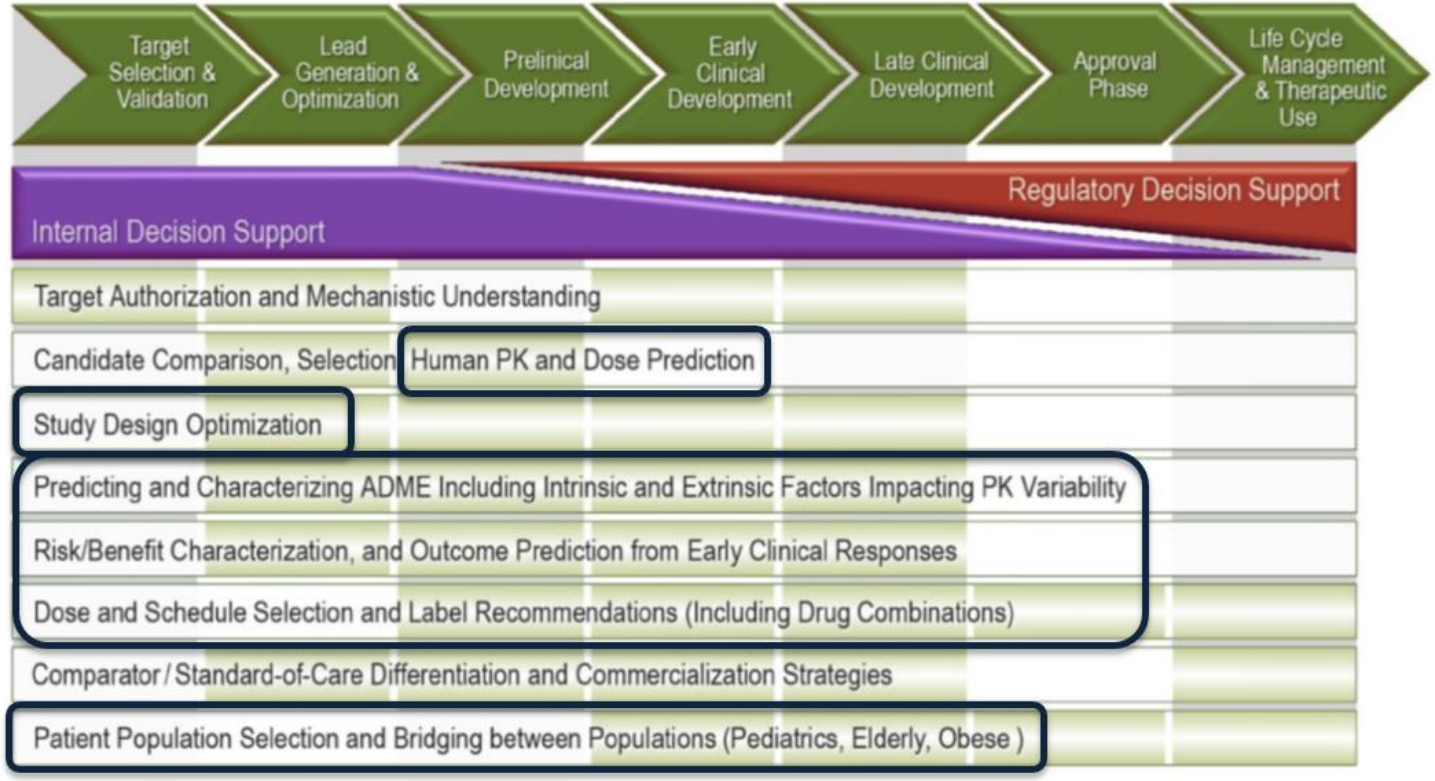
# What is MIDD? (cont..)




*Bruno 2019 [PMID 30951201]*

*PK – Pharmacokinetics; POPPK – Population Pharmacokinetics; PBPK – Physiologically-based pharmacokinetics*
*PK/PD – Pharmacokinetics/Pharmacodynamics; QSP – Quantitative Systems Pharmacology;*
*QSAR – Quantitative Structure-Activity Relationship; QSPKR – Quantitative Structure-Pharmacokinetics Relationships*

# Value of MIDD





*Marshall 2016 [PMID 27069774] | Wang 2019 [PMID 30653670]*

# Push-Pull forces on MIDD

## Enablers

- Acceptance by multidisciplinary teams
- Environment that fosters collaboration
- Organizational alignment, prioritization and support
- Education and training
- Methodological advancement

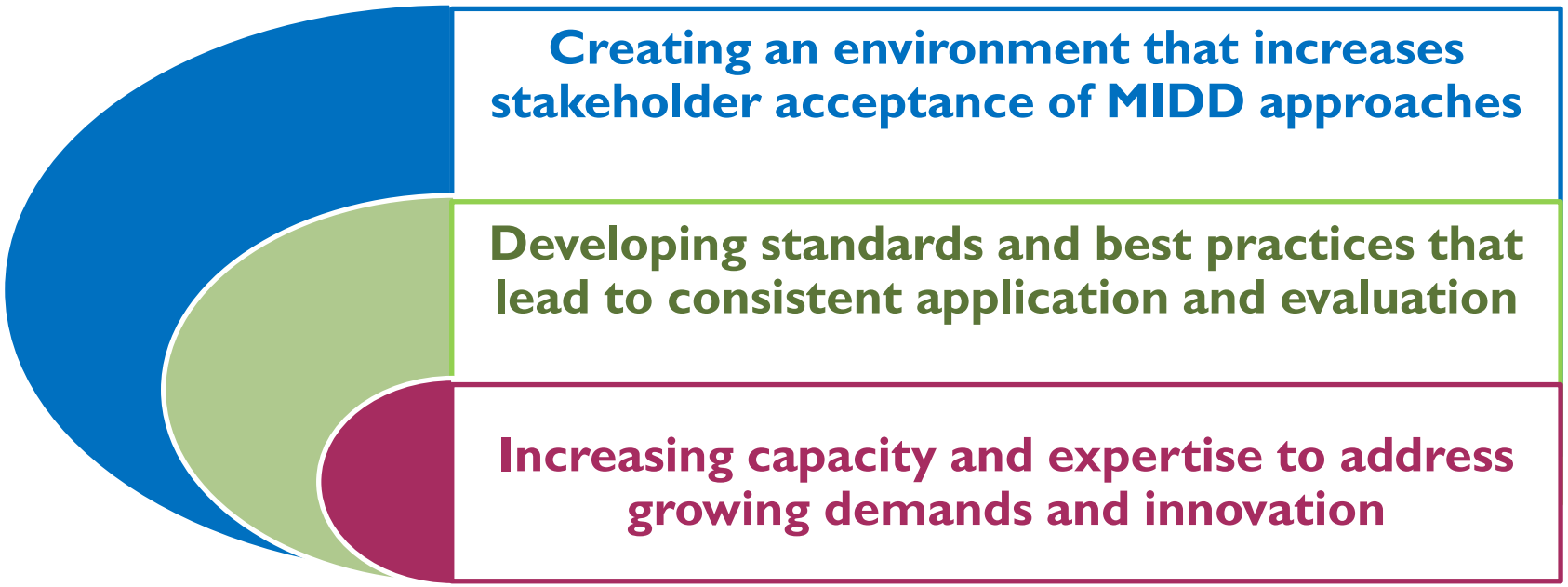
## Challenges

- Identification and transparent communication of knowledge gaps
- Best practices for determining a model is fit-for-purpose
- Data/Knowledge warehouses
- Varying degrees of comfort by end-users
- Clarity on regulatory expectations

*Madabushi 2019 [PMID 31081932] | Marshall 2019 [PMID 30411538]*

# Advancing MIDD

*A Holistic and Integrative Approach*




Madabushi 2019 [PMID 31081932]

Creating an environment that increases stakeholder acceptance of MIDD approaches

Developing standards and best practices that lead to consistent application and evaluation

**Increasing capacity and expertise to address growing demands and innovation**

# PBPK in Regulatory Submissions

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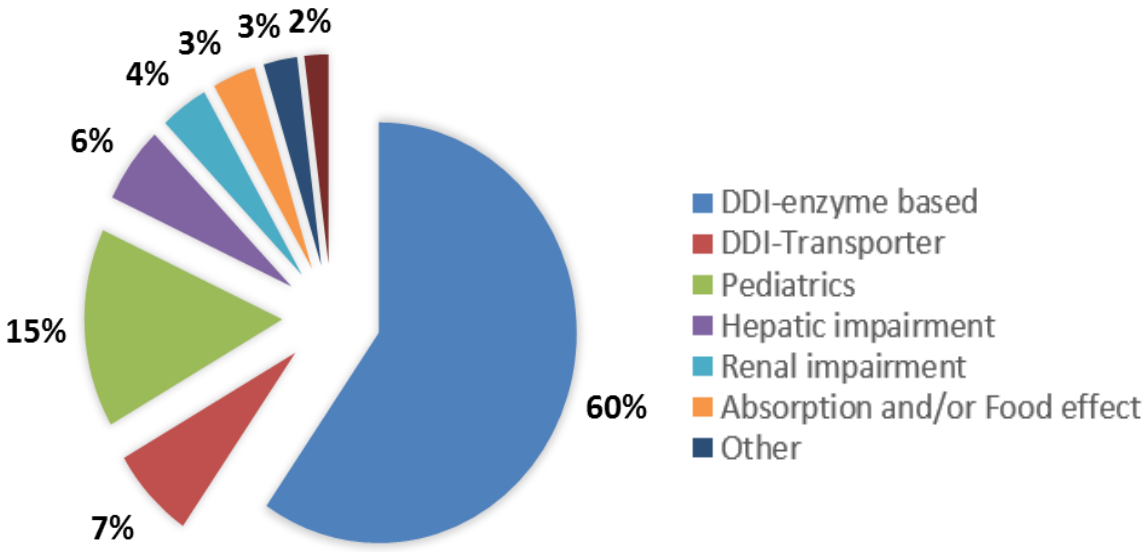
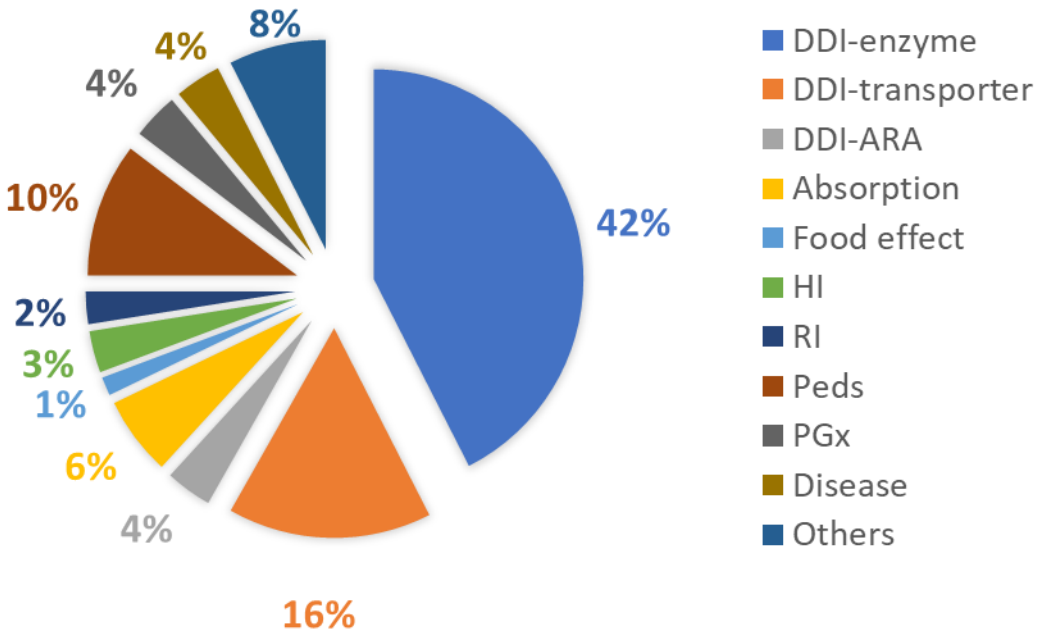
## 2008-2017 (n=254)



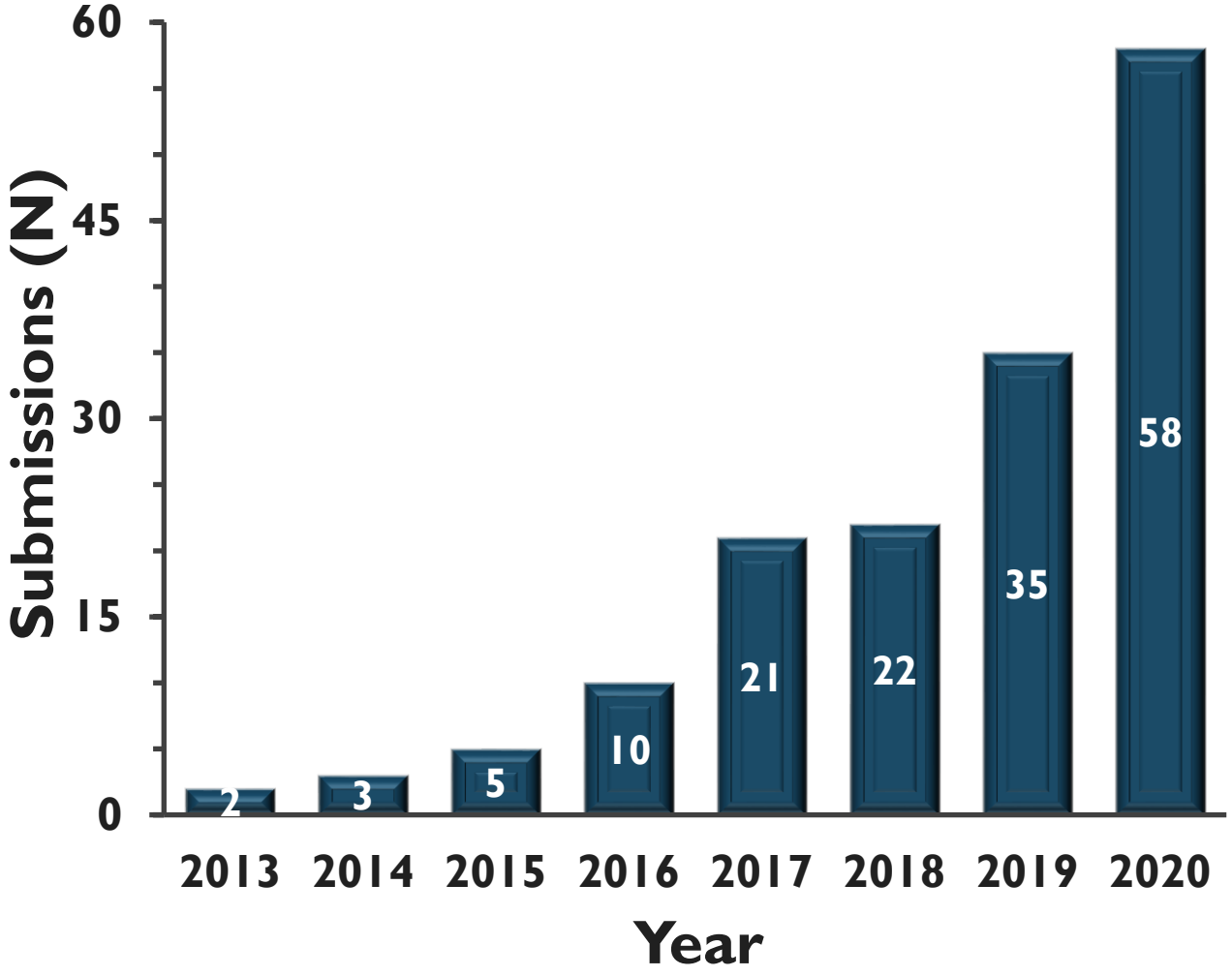

## 2018-2020 (n=174)

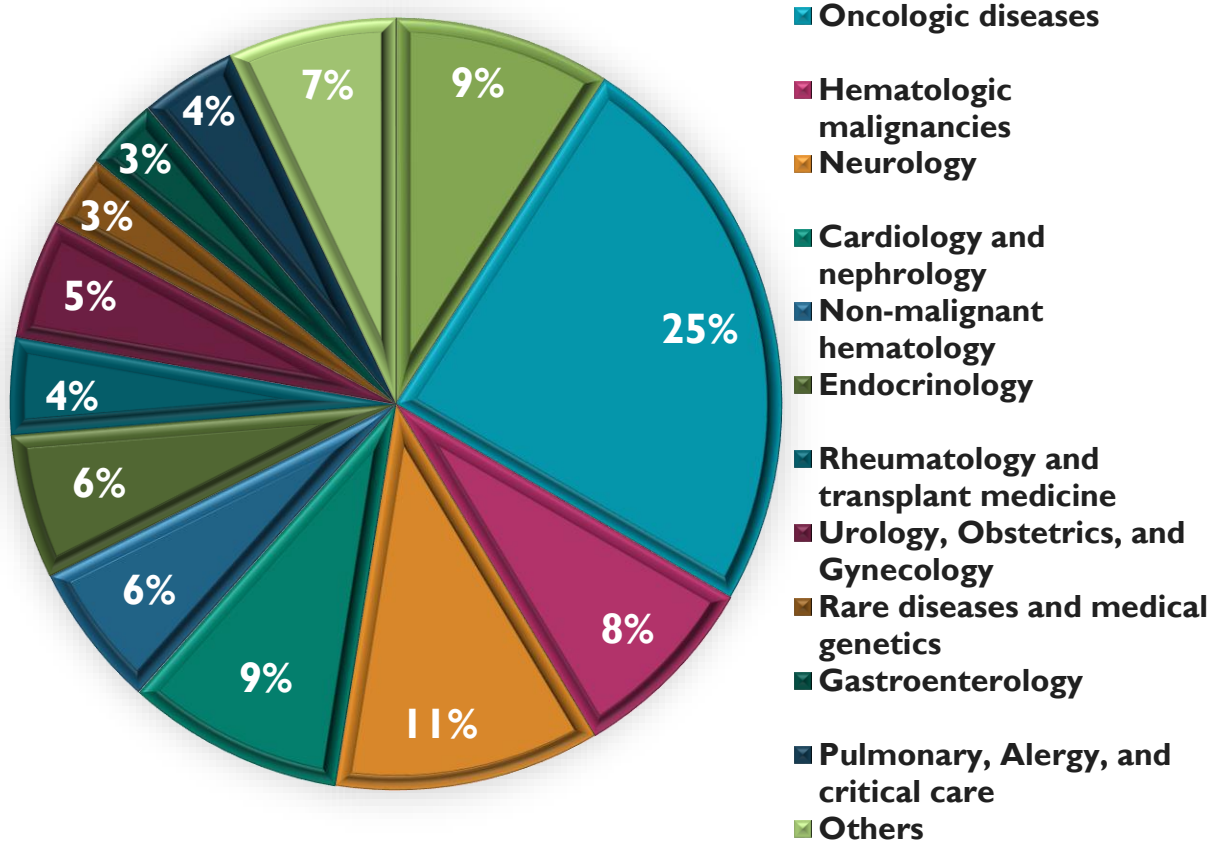



*Grimstein, 2019 [PMID: 30385284]; Zhang 2020 [PMID: 33205429]*

*Courtesy: Xinyuan (Suzie) Zhang*

# QSP in Regulatory Submissions




*Bai, 2021 [PMID: 34734497]*

# AI/ML and RWE Activities in OCP/FDA

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## Innovative Data Analytics (IDA) Program

- EDUCATION
- RESEARCH
- COLLABORATION
- FELLOWSHIP

AI/MACHINE LEARNING | DIGITAL HEALTH TOOLS | REAL WORLD EVIDENCE | OTHER


*Courtesy: Qi Liu*

Creating an environment that increases stakeholder acceptance of MIDD approaches

**Developing standards and best practices that lead to consistent application and evaluation**

Increasing capacity and expertise to address growing demands and innovation

# MIDD Workshops

## *Engaging Stakeholders and Developing Best Practices*

U.S. FOOD & DRUG ADMINISTRATION

**FDA-ISoP Public Workshop: Model Informed Drug Development (MIDD) for Oncology Products**

SHARE TWEET LINKEDIN PIN IT EMAIL PRINT

Co-sponsored by the:
U.S. Food & Drug Administration (FDA) and the International Society of Pharmacometrics (IsoP)

WORKSHOP

**Precision Dosing: Defining the Need and Approaches to Deliver Individualized Drug Dosing in the Real-World Setting**

AUGUST 12, 2019

**Pediatric Ontogeny: Ready for Incorporation into Modeling in Pediatric Drug Development?**

**Development of Best Practices in Physiologically Based Pharmacokinetic Modeling to Support Clinical Pharmacology Regulatory Decision-Making**

NOVEMBER 18, 2019

WORKSHOP

**Public Workshop on Clinical Pharmacology in Drug Development for Nonalcoholic Steatohepatitis (NASH) and Cholestatic Liver Diseases**

DECEMBER 9, 2019

PUBLIC

**Assessing Changes in Pharmacokinetics of Drugs in Liver Disease**

OCTOBER 8, 2020

PUBLIC

**FDA Public Workshop: Pediatric Dose Selection**

OCTOBER 22 - 23, 2020

WORKSHOP

**Roadmap to 2030 for New Drug Evaluation in Older Adults**

MARCH 23, 2021

PUBLIC

**Model Informed Drug Development Approaches for Immunogenicity Assessments**

JUNE 9, 2021

VIRTUAL

**Fetal Pharmacology and Therapeutics October 21 - 22, 2021**

OCTOBER 21 - 22, 2021

VIRTUAL

**Pharmacodynamic Biomarkers for Biosimilar Development and Approval**

SEPTEMBER 20 - 21, 2021

PUBLIC

**Best Practices for Development and Application of Disease Progression Models**

NOVEMBER 19, 2021

PUBLIC

**FDA and Center for Research on Complex Generics Co-Hosted Workshop: Establishing the Suitability of Model-Integrated Evidence to Demonstrate Bioequivalence for Long-Acting Injectable and Implantable Drug Products**

NOVEMBER 30, 2021

WORKSHOP

**Drug Permeability: Best Practices for Biopharmaceutics Classification System-Based Biowaivers**

DECEMBER 6, 2021

# MIDD Guidance Efforts

*Providing clarity on regulatory expectations*

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GUIDANCE DOCUMENT

**Physiologically Based Pharmacokinetic Analyses – Format and Content Guidance for Industry**

SEPTEMBER 2018

Download the Final Guidance Document

Final

GUIDANCE DOCUMENT

**Drugs for Treatment of Partial Onset Seizures: Full Extrapolation of Efficacy from Adults to Pediatric Patients 2 Years of Age and Older Guidance for Industry**

SEPTEMBER 2019

Download the Final Guidance Document | Read the Federal Register Notice

Final

GUIDANCE DOCUMENT

**Pharmacokinetic-Based Criteria for Supporting Alternative Dosing Regimens of Programmed Cell Death Receptor-1 (PD-1) or Programmed Cell Death-Ligand 1 (PD-L1) Blocking Antibodies for Treatment of Patients with Cancer**

*Draft Guidance for Industry*

AUGUST 2021

Download the Draft Guidance Document | Read the Federal Register Notice

Draft

GUIDANCE DOCUMENT

**Population Pharmacokinetics**

*Guidance for Industry*

FEBRUARY 2022

Download the Final Guidance Document

Final | Level 1 Guidance

**New areas of ICH harmonisation**

The ICH Assembly supported and endorsed the revised New Topic proposal and associated Concept Paper Outline on General Considerations for Model-Informed Drug Development (MIDD) for establishment of a M15 informal WG.

**Creating an environment that increases stakeholder acceptance of MIDD approaches**

Developing standards and best practices that lead to consistent application and evaluation

Increasing capacity and expertise to address growing demands and innovation

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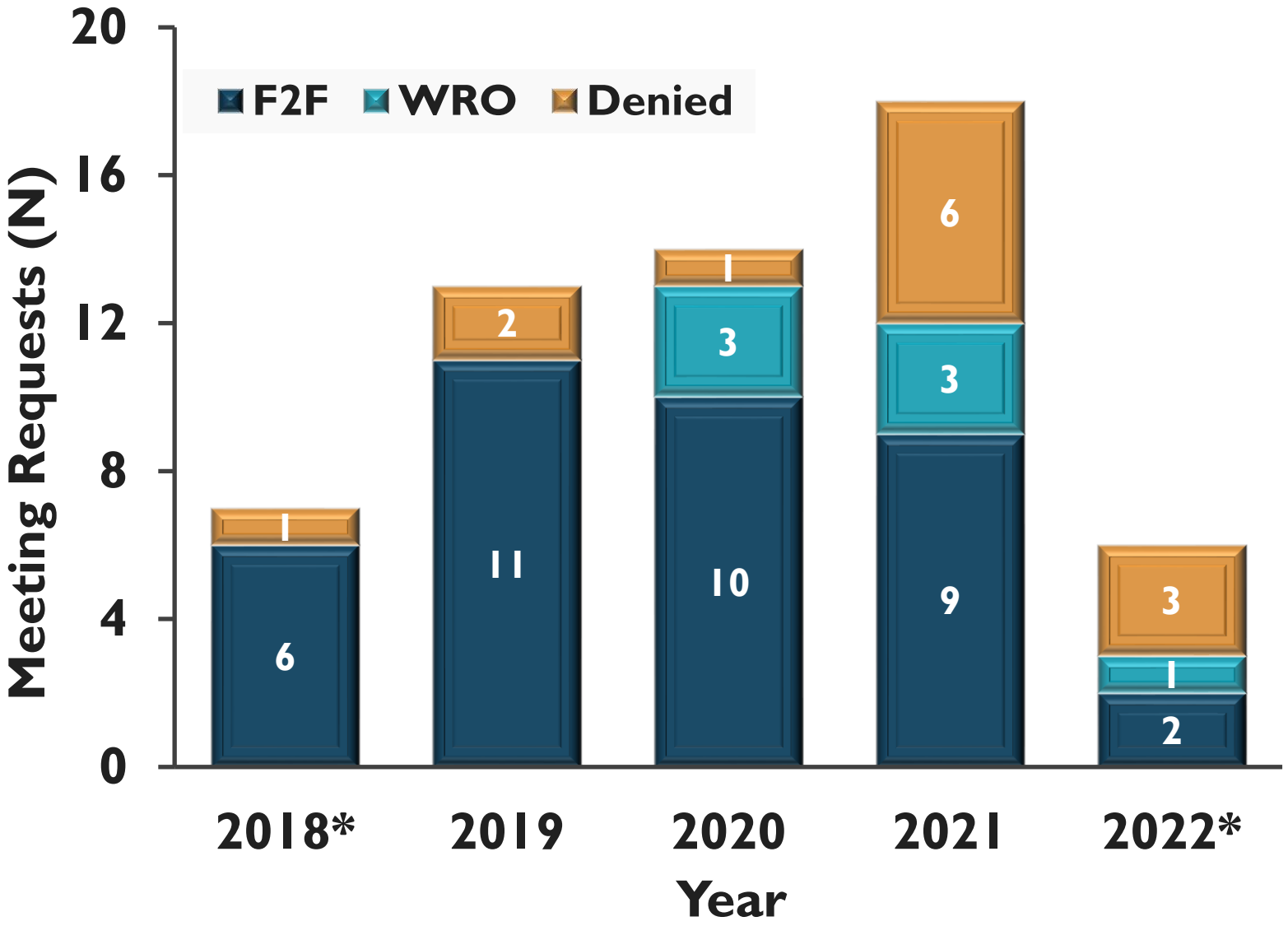
# MIDD Paired Meeting Pilot Program

# MIDD Paired Meeting Pilot Program

- The MIDD Pilot Program is jointly administered by:
  - CDER's Office of Clinical Pharmacology
  - CBER's Office of Biostatistics and Epidemiology
- A dedicated forum for regulatory interaction on MIDD
  - To provide advice on how proposed MIDD approaches can be used in a specific drug development program to address issues
    - Dose selection/optimization,
    - Clinical trial simulation, and
    - Mechanistic safety evaluation
  - Granted requests involve up to a pair of meetings

*MIDD Website - https://www.fda.gov/drugs/development-resources/model-informed-drug-development-pilot-program*

# Clear Demand for the Program and Increasing




**58** Meeting Requests
28 Sponsors

**45** Granted
7 WROs; 38 F2F

**46** Sponsor Meetings¤
19 meetings avoided

**112** Internal Meetings¤
>2x effort in preparation

* *Partial year #s*

¤ *Conducted as of Dec 31, 2021*

# Program Experience

## *Requests Span Drug Development and Therapeutic Areas*

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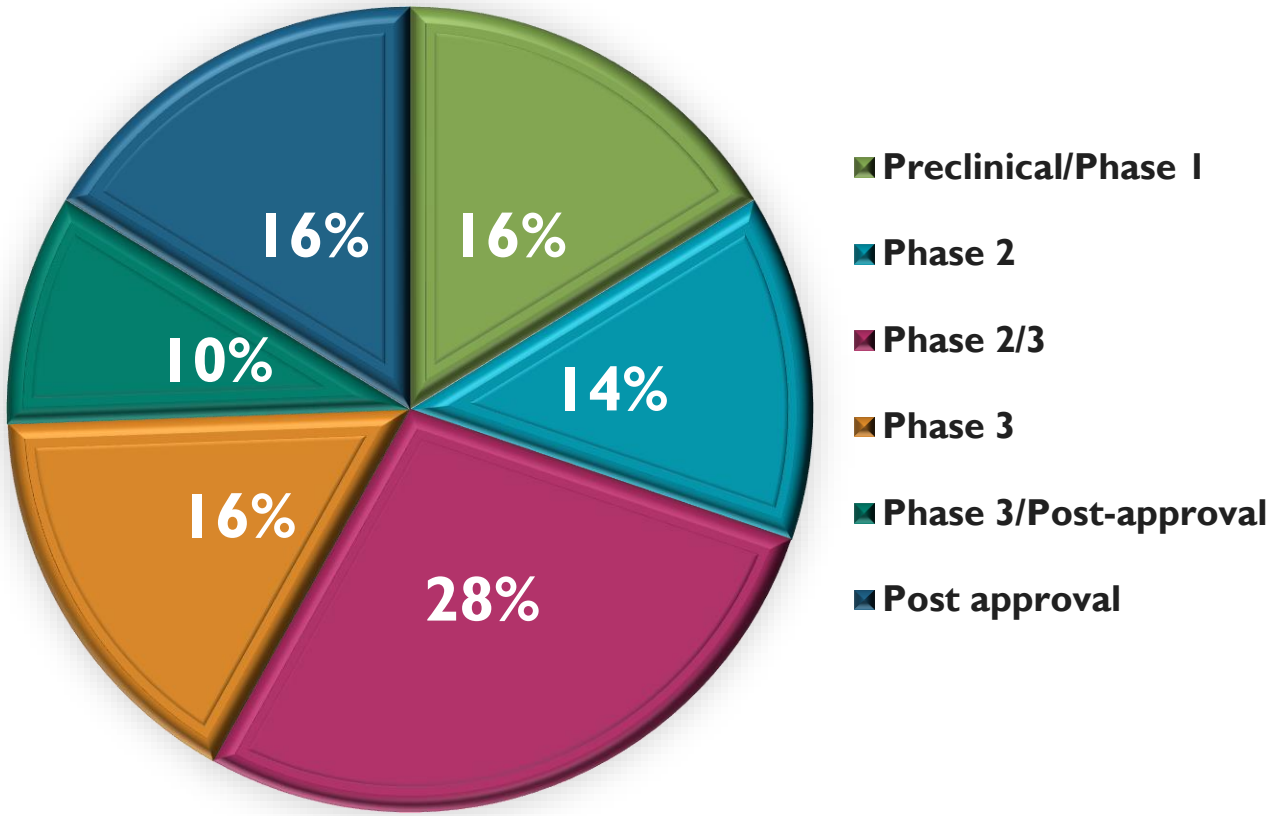
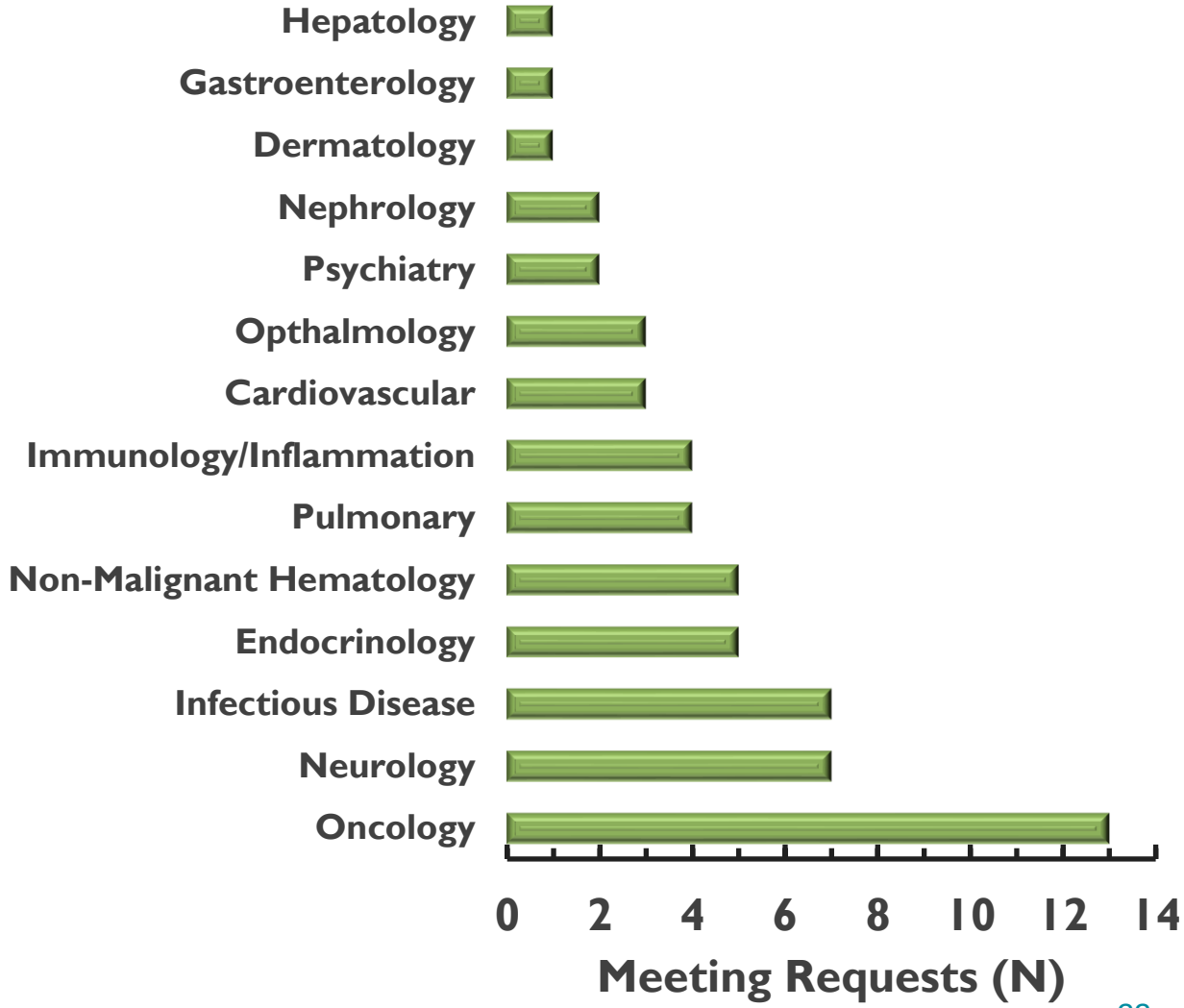
### Development Phase




### Therapeutic Areas



# Methods and Applications

*Variety of MIDD Methods for Targeted Applications*

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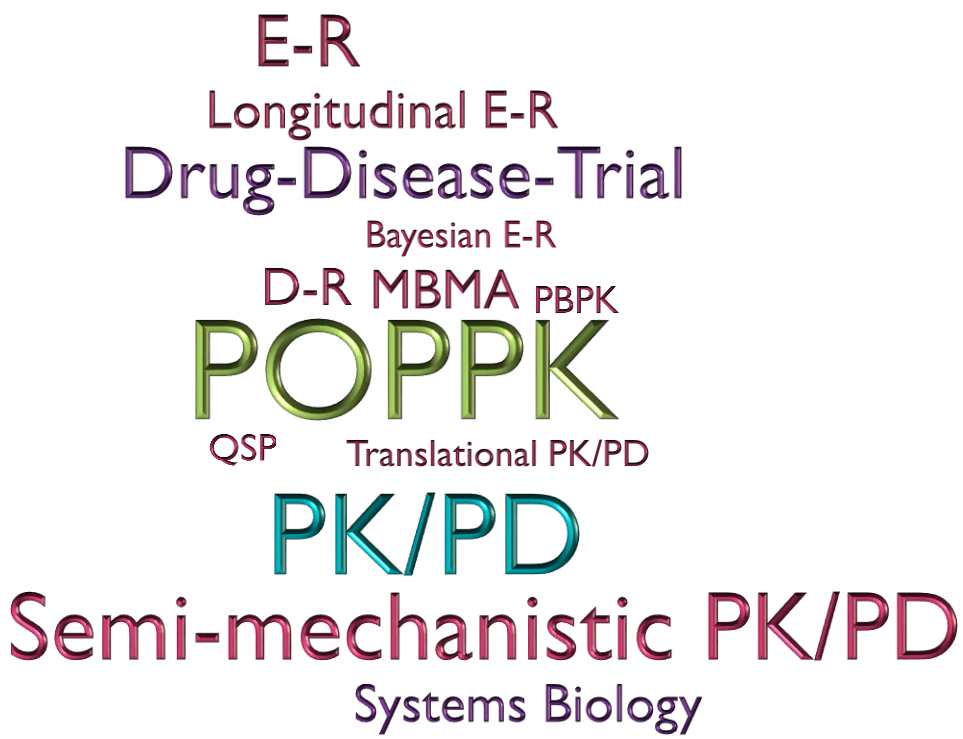
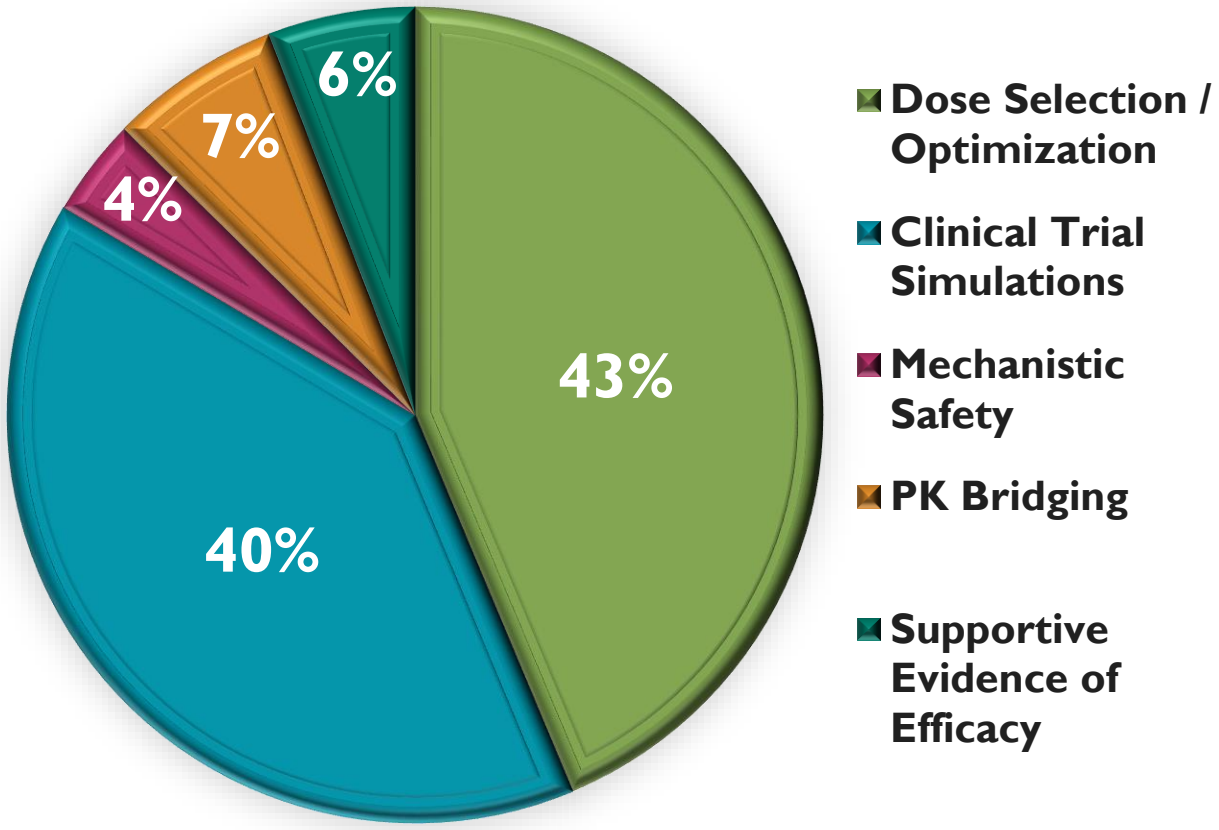
## MIDD Methods



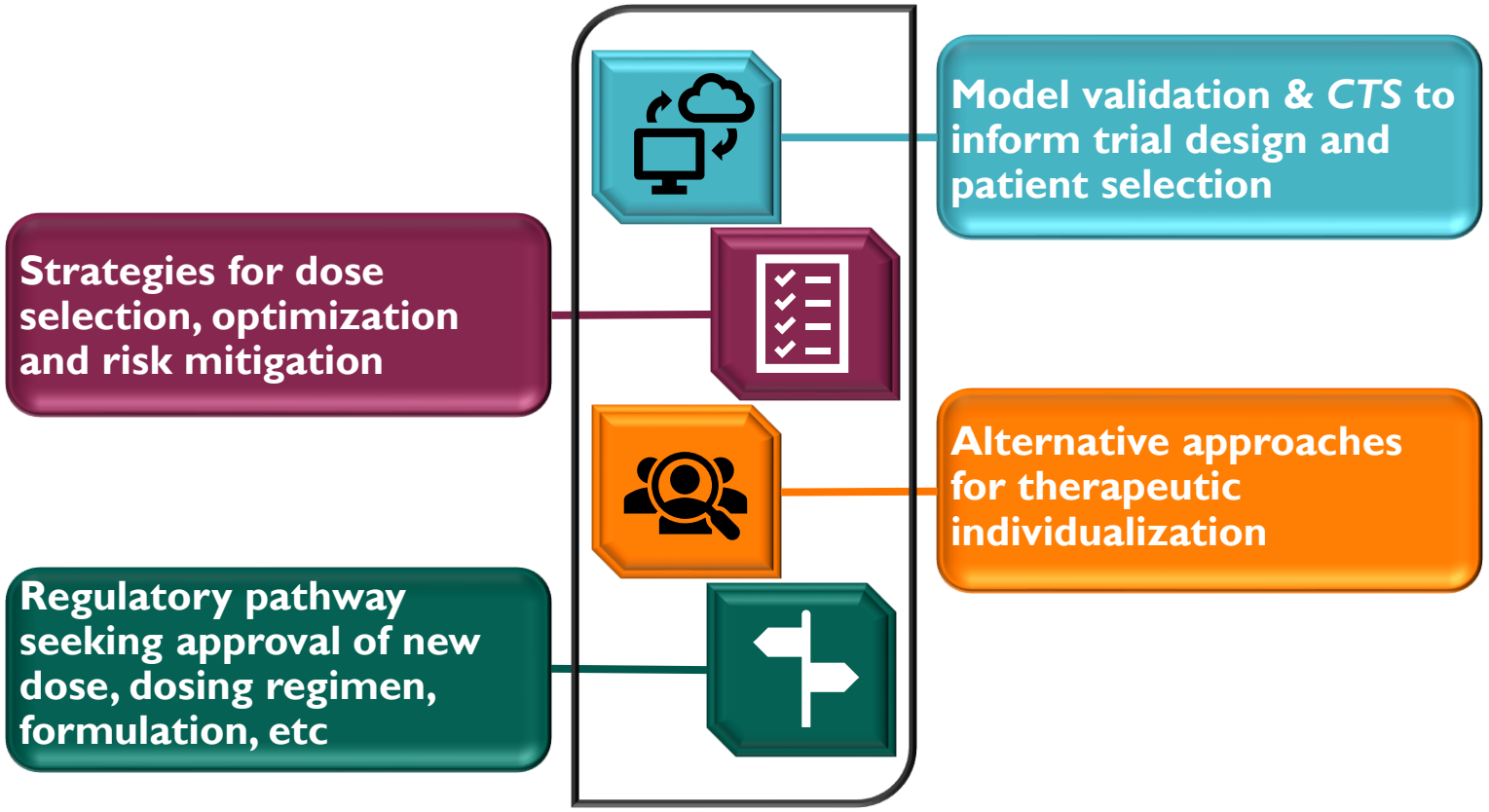

## MIDD Applications



# Impact

## *Targeted Applications Resulting in Alignment on Regulatory Pathway*

### Drug Development




### Regulatory Approvals

- **Ramucirumab**
  Approval of shorter infusion option
- **Sotalol Hydrochloride**
  Approval of a new dosing strategy that reduces the hospital stay
- **Cetuximab**
  Approval of a dosing regimen with extended inter-dosing interval
- **Valbenazine**
  Approval of a new dose option as part of titration

*Full prescribing information is available at*
https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022306s005lblrpl.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125477s036lbl.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125084s277s280lbl.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/209241s020lbl.pdf

# Impact

## *Case Example - Sotalol IV*

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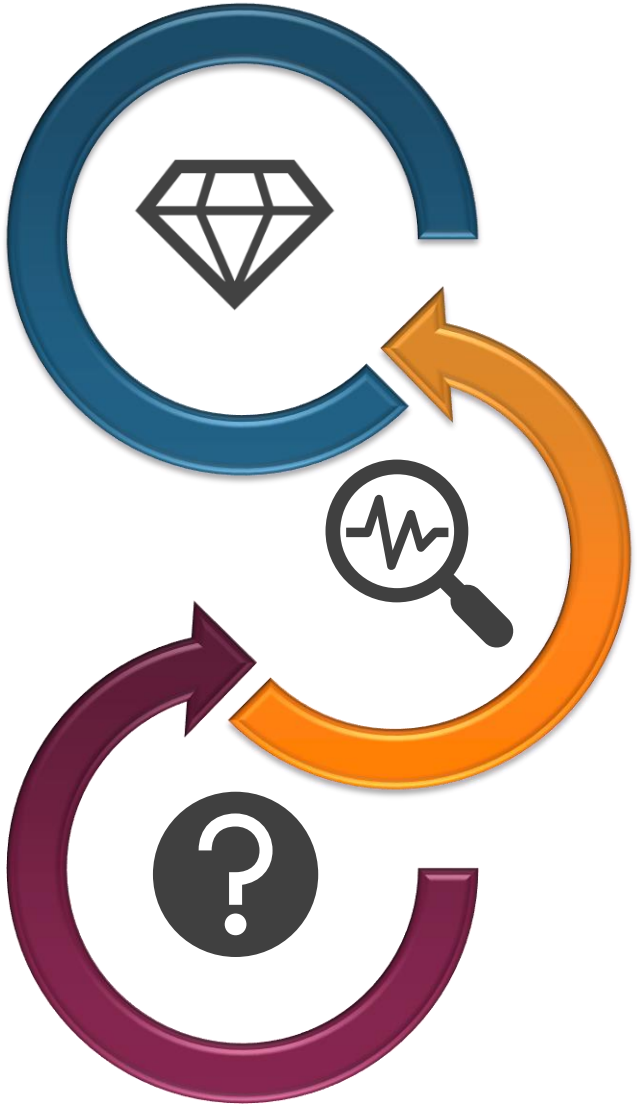
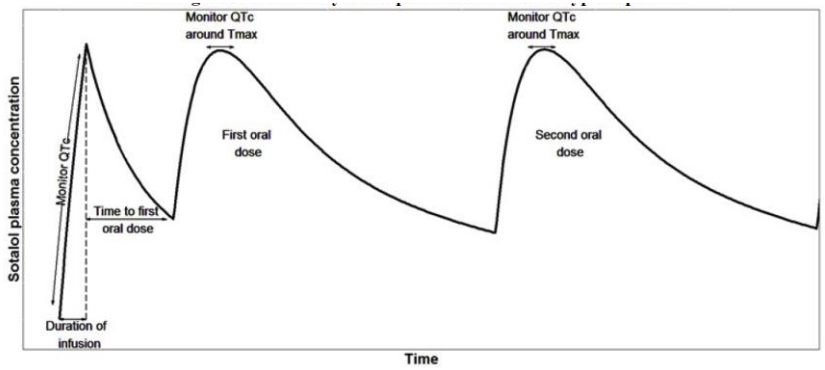
### Evaluation

- Acceptability of PK and QTc modeling and simulation approach;
- Acceptability of QTc monitoring plan, loading dose, initiation of oral maintenance dosing, discontinuation and re-initiation strategy;
- Dosing strategy across the range of renal function



### Outcome

- Approval of a new dosing strategy based on PK/PD modeling and simulation;
- Reduces the hospital stay by 1 day
- Dosing over the range of renal function




### Issue

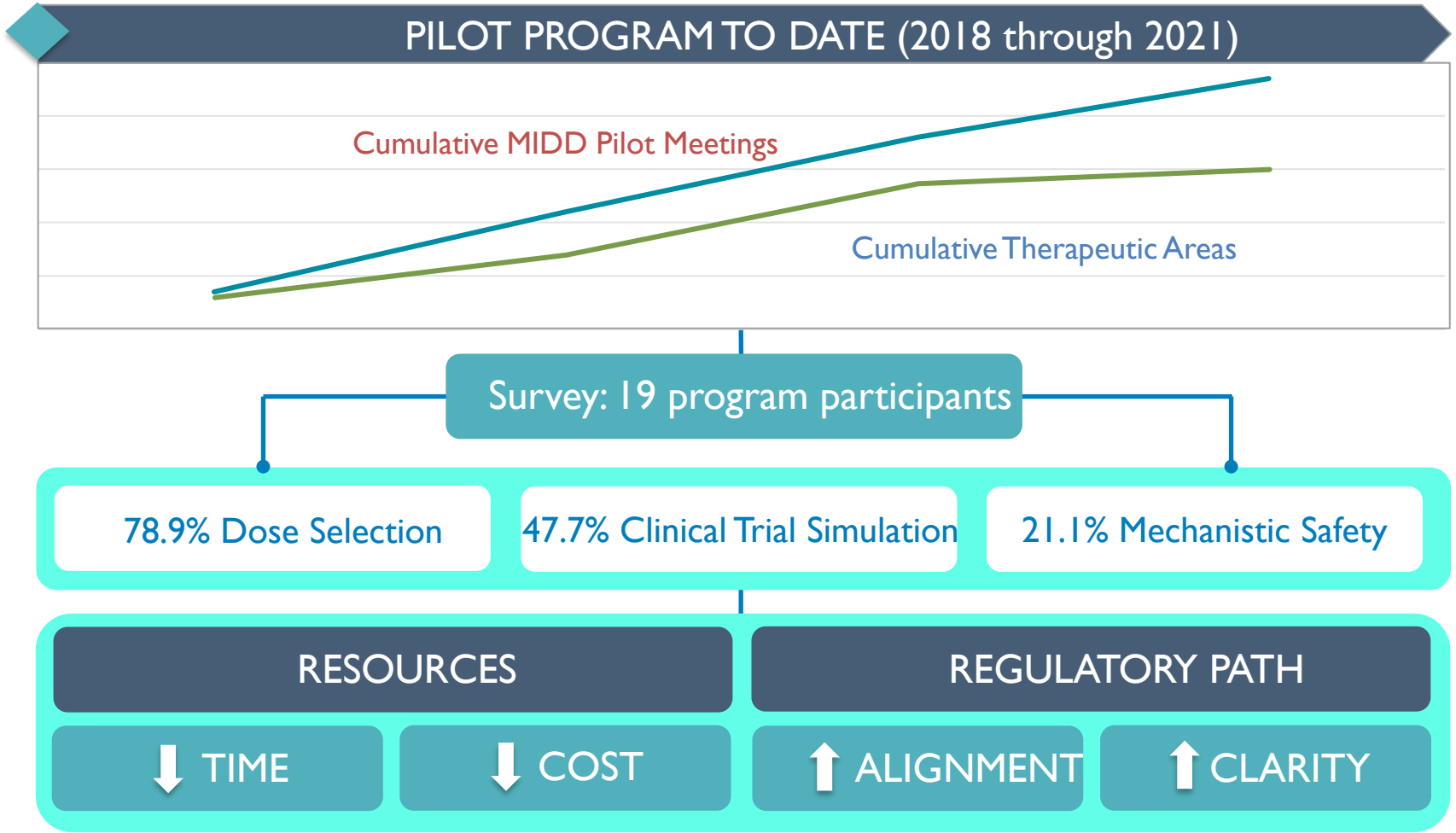
- Label change for IV loading and dose escalation for sotalol to quickly achieve peak steady-state ;
- SoC – Sotalol initiation in a new patient involves a hospital stay of 3 days

*Full prescribing information is available at https://go.usa.gov/xdJQe*

*News Release*

# MIDD Pilot Program

## *Industrial Benefit*




*Source: Results from International Consortium for Innovation and Quality in Pharmaceutical Development survey Clin Pharmacol Ther 2021;110(5):1172-1175*

Slide Courtesy: Kim Bergman & Issam Zineh

# MIDD Pilot Program

## *Industrial Benefit*

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### TIME

- Accelerated timelines (months to years to infinite savings)
- Informed go/no-go decisions
- Supportive M/S
- Totality of evidence
- Reduced N, faster recruitment
- New pathways for approval

### COST

- Savings est. up to $30-70M
- Smaller (reduced) trials
- M/S replacing trials
- Getting to the right dose faster
- Leveraging PK/PD on less costly biomarkers
- Path to potential new indications
- *Priceless*

### ALIGNMENT

- Study design
- Intended disease
- Model-based dose selection
- Population
- Technical feasibility
- Traction gained
- Interactions with key experts
- *Confidence/trust*

### CLARITY

- Direct feedback
- Additional data needed for further development and approval
- Technical expectations
- SME discussions
- Engaged scrutiny
- *Confidence/trust*

Slide Courtesy: Kim Bergman & Issam Zineh

# What next?

# MIDD under PDUFA VII

FDA will build on the success of the "model-informed drug development" (MIDD):

- By no later than the end of 1st Quarter of FY 2023, FDA will publish a Federal Register Notice announcing the **continuation of the MIDD paired meeting program**, outlining program eligibility, and describing the proposal submission and selection process.
- FDA will grant a pair of meetings specifically designed for this program, consisting of an initial and a follow-up meeting on the same drug development issues. The second meeting will occur within approximately 60 days of receiving the briefing materials.
- Starting in FY 2023, FDA will select 1-2 eligible and appropriate proposals per quarter each year (i.e. up to 8 per year). Additional proposals that meet the eligibility criteria may be selected depending upon the availability of resources.
- FDA will issue a **Request for Information (RFI)** to elicit public input for identifying priority focus areas for future policy or guidance development and stakeholder engagement. This RFI will be issued by no later than the end of FY 2024.

*PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2023 THROUGH 2027*

# Summary

- MIDD is a critical component of the toolkit to address the challenges of drug development
- A holistic and integrative approach is critical to enable and advance MIDD
  - to address growing demands and innovation
  - to ensure consistent application and evaluation
  - to increase stakeholder acceptance
- The initiatives under PDUFA demonstrate tangible benefits to drug development and regulatory decision-making

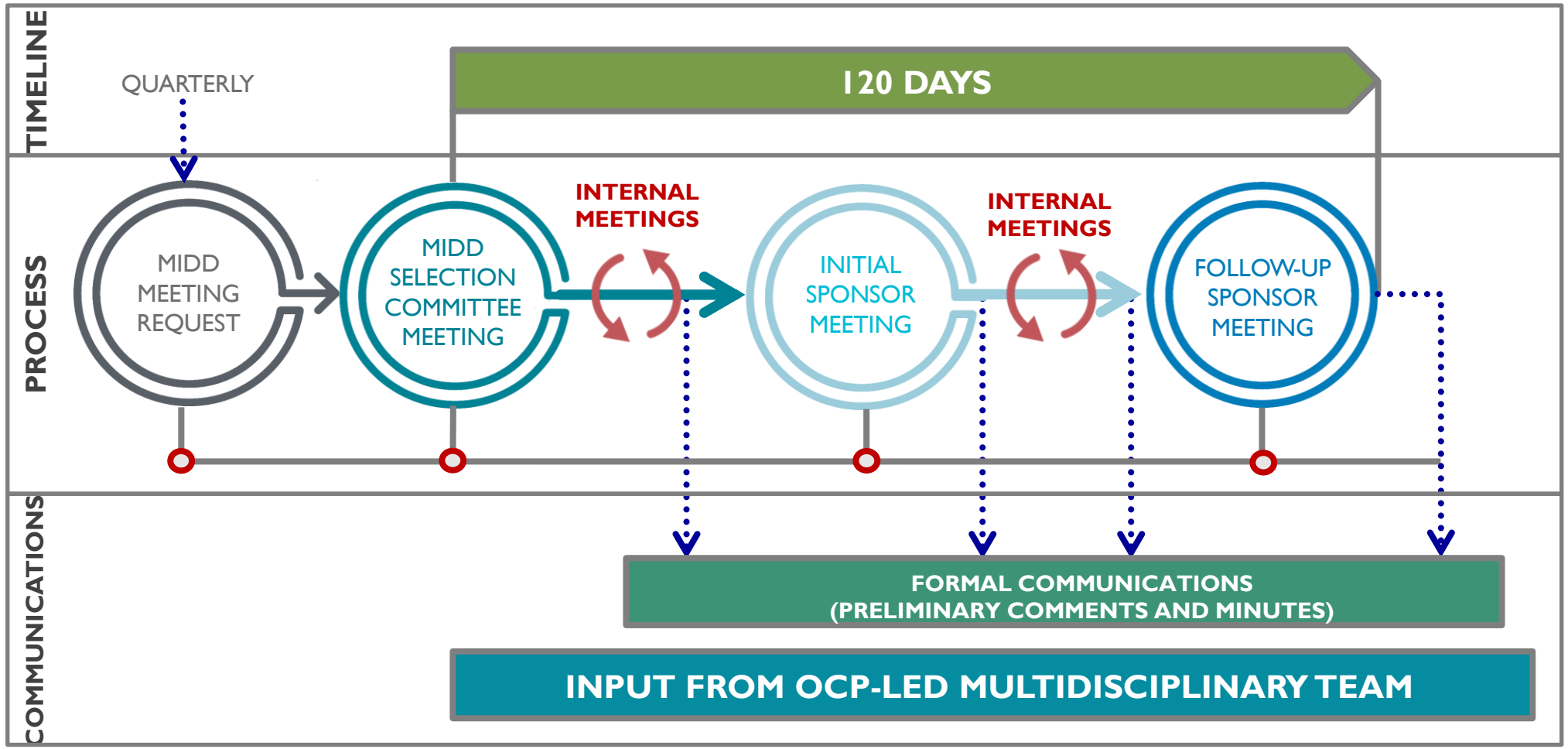
# Thank You!


## Acknowledgements

- Issam Zineh – Director, Office of Clinical Pharmacology
- Jessica Benjamin – Associate Director, Regulatory Affairs
- Yvonne Knight – Executive Program and Project Management
- Kim Bergman – Strategic Communications
- Kunal Naik – Executive Program and Project Management
- Jeffry Florian – Division of Applied Regulatory Science
- MIDD Steering Committee, MIDD Selection Committee
- Pilot Program Participants
  – Sponsors, CDER/CBER Staff

# Backup

# MIDD Paired Meeting Overview




Courtesy: Kimberly Bergman