CLOSING PANEL DISCUSSION

FDA U.S. FOOD & DRUG ADMINISTRATION

AACR American Association for Cancer Research®

FDA-AACR Public Workshop On
OPTIMIZING DOSAGES FOR ONCOLOGY DRUG PRODUCTS: QUANTITATIVE APPROACHES TO SELECT DOSAGES FOR CLINICAL TRIALS
February 15 and 16, 2024 I Washington, DC

Closing Remarks and Panel Discussion

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Draft Guidance – January 2023

Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases

Guidance for Industry

DRAFT GUIDANCE

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
January 2023
Clinical/Medical

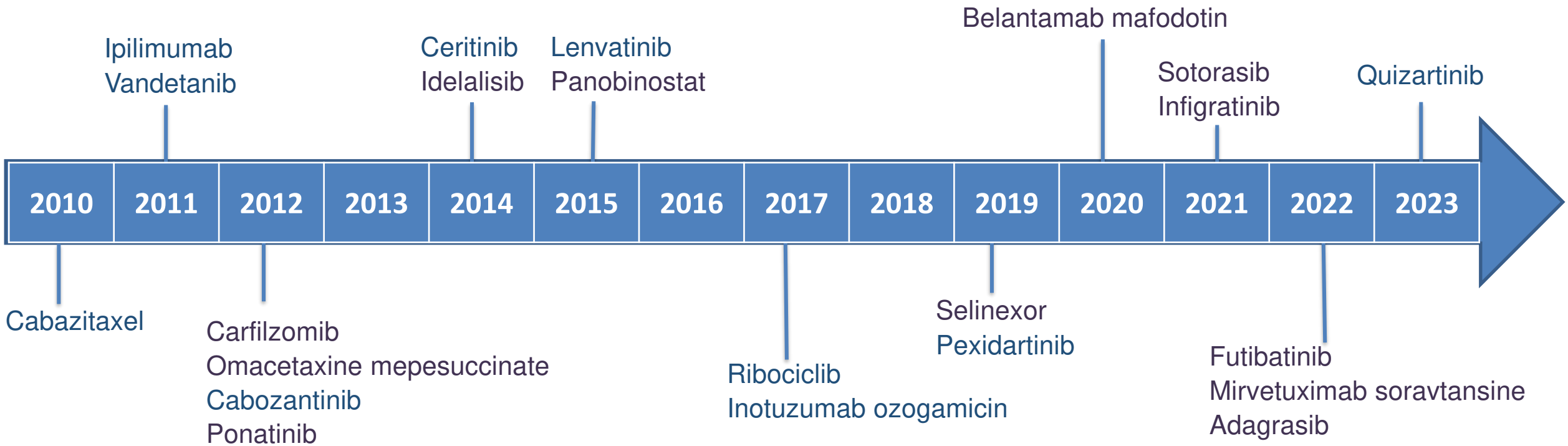
Why Project Optimus

Consequences of Not Optimizing Dosage Before Approval

- Drug is poorly-tolerated at approved recommended dosage
  - Patients may stop taking a potentially effective drug
  - Patients choose to try a different drug
- Drug does not make it to market or must be withdrawn from the market
- Takes long time to evaluate alternative dosages following approval
  - Patients may not want to participate in trial if commercially available
  - Disease area moves on to other treatments
- **The Challenge**: Identify the Best Tolerable Dose: The dose that is best tolerated without compromising efficacy

Dosage Optimization PMRs

- 24 PMRs issued for 21 new drugs (15% of 138 total approved new drugs)
- Took a median of 6.5 years to fulfill or release



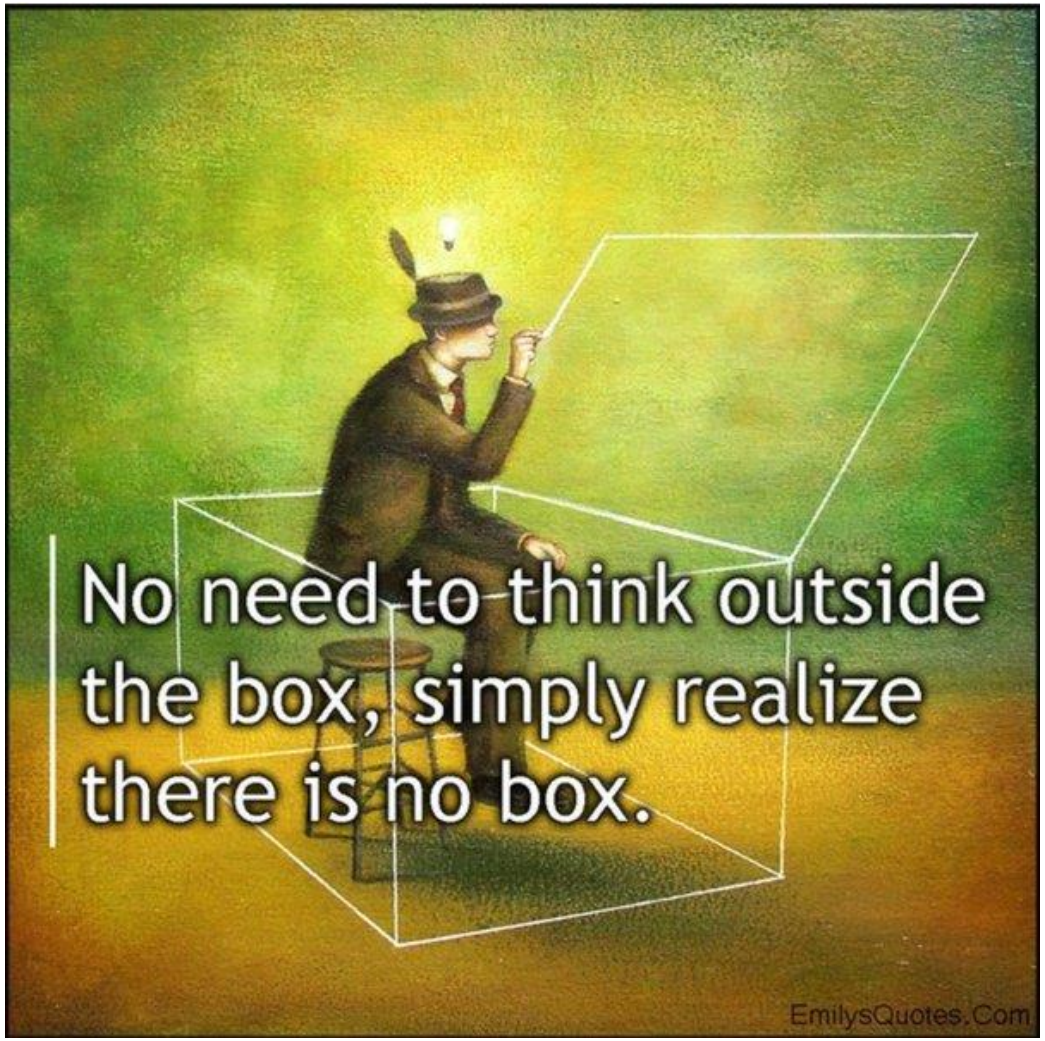
Publication: Journal of Clinical Oncology Volume 41, Number 16_suppl https://doi.org/10.1200/JCO.2023.41.16_suppl.159

Project Optimus

Novel Approaches:

- Many examples and tools we saw over the past 1.5 days
  - Developed before Project Optimus
- Many developed very creatively – “fit for purpose”
- Question:
  - How do we create space for creativity in trial design while minimizing tension?

We Need to Go "Beyond the Box"



One Size Does Not Always Fit All

New Paradigm Emphasizes Focusing on Dosage Optimization Prior to Approval

- 'Optimized' dosage in registration trial
  - Improves tolerability and adherence
  - Reduces dosage modifications (i.e., discontinuations)
  - And potentially increases likelihood of greater response to treatment
- Earlier understanding of dose- and exposure-response relationships may speed up novel therapy development
- More efficient to evaluate multiple dosages early in development
- Challenge:
  - Making sure we have the right dose for both safety AND efficacy
  - Difficult to conduct dosage optimization trials one a drug is approved

Project Optimus Supports Evaluating All Data to Inform Dosage Selection for Clinical Trials

- **Consider all data**: pharmacokinetic (PK), pharmacodynamic (PD), activity/efficacy, safety, and tolerability data at each step
- **Evaluate safety information beyond DLTs**, e.g., low-grade symptomatic toxicities, dosage modification frequencies, patient-generated data for treatment-related symptoms
- **Identify a target dosage range early** and then further evaluate several dosages (ideally in a randomized trial)
- **Characterize dosage-** and exposure-response relationships for efficacy and toxicity

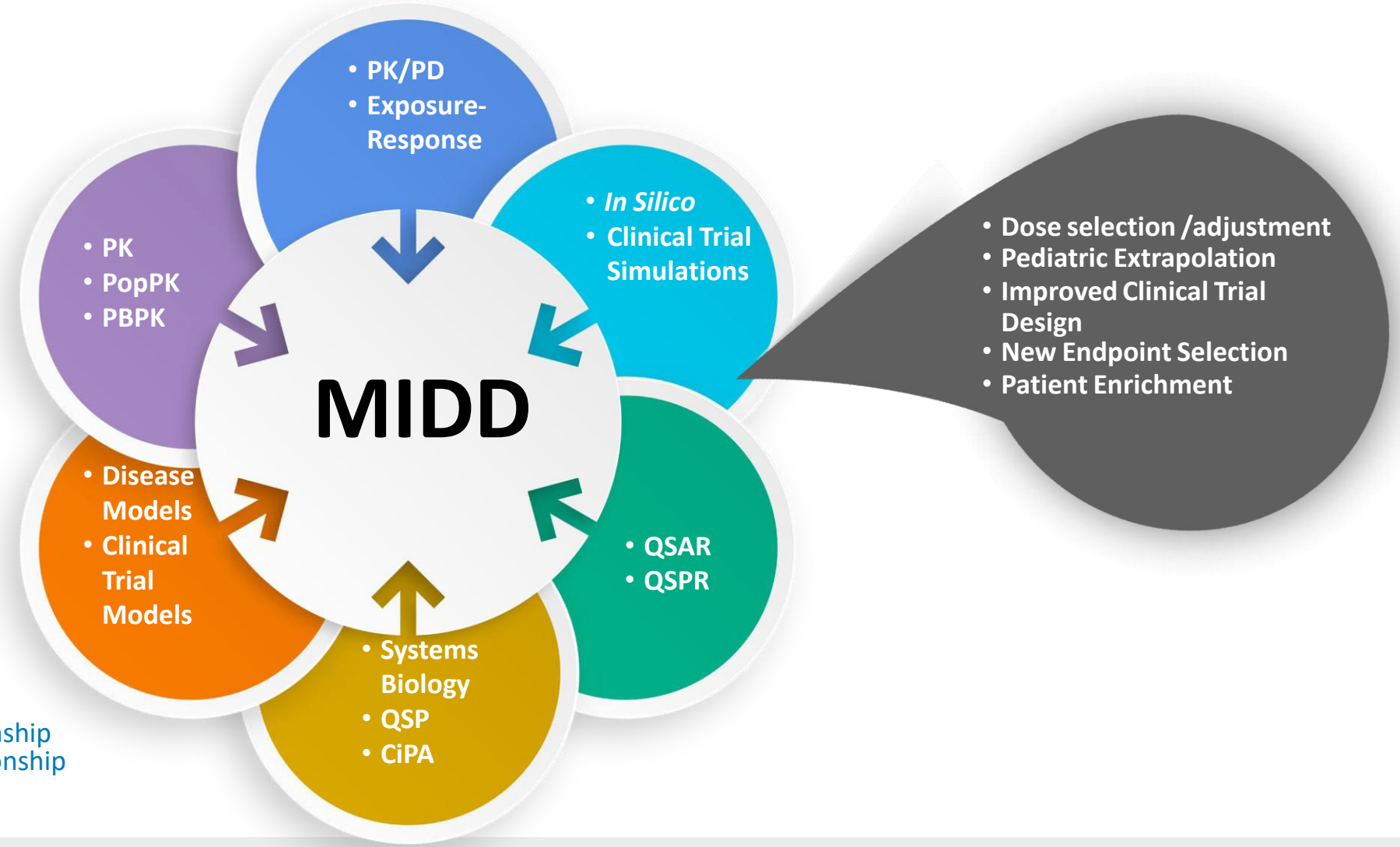
Are we trying to establish a primary development process for each agent?

I don't think so

Multi-disciplinary Collaboration is Necessary

Model-Informed Drug Development

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



QSAR: Quantitative structure–activity relationship
QSPR: Quantitative structure–property relationship

Huang SM 2019 AAPS

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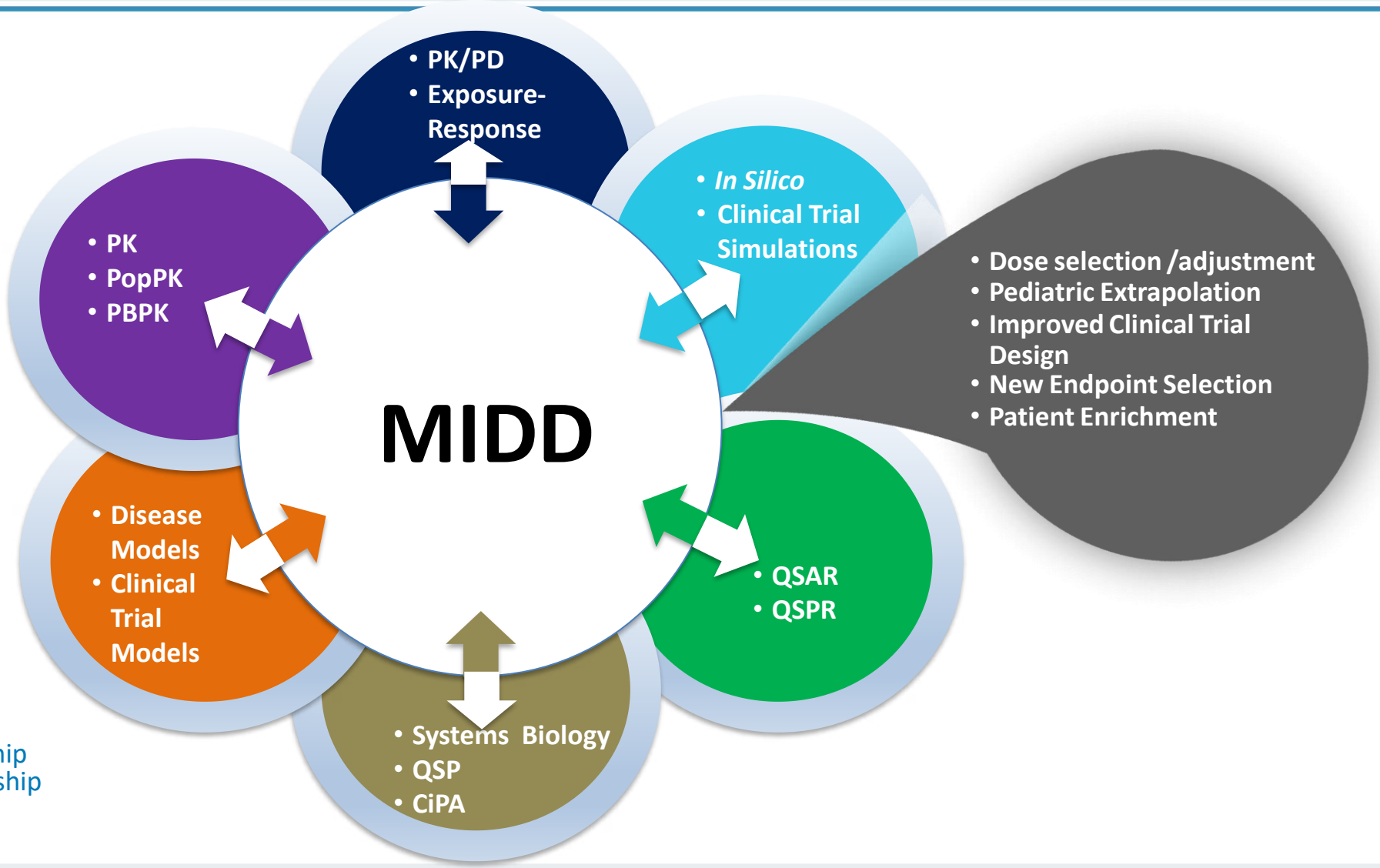

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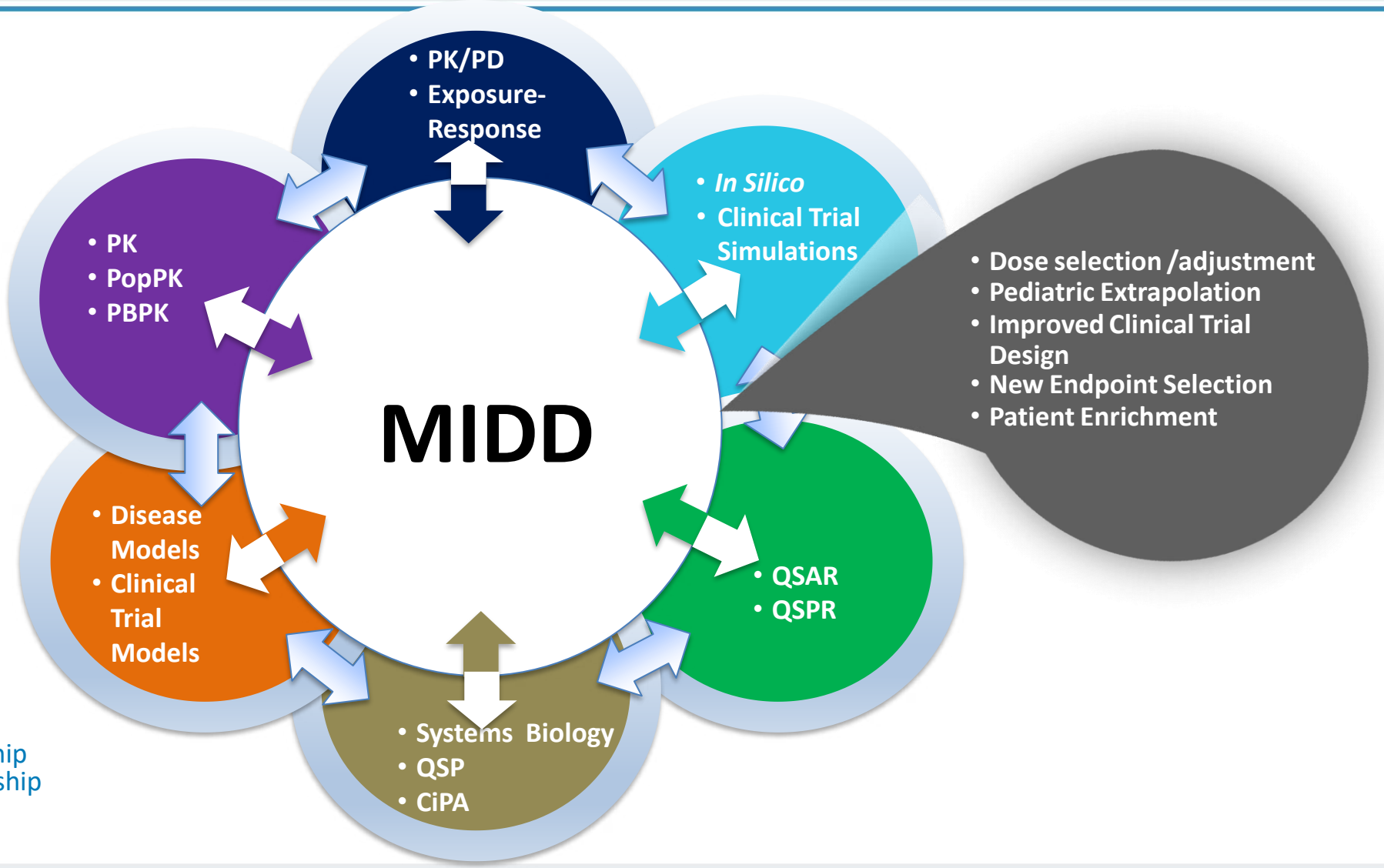

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CLOSING REMARKS, LESSONS LEARNED AND NEXT STEPS

MODERATOR

Patricia M. LoRusso, DO, PhD (hc), FAACR
Yale Cancer Center

ADDITIONAL PANELISTS

Atiqur Rahman, PhD
U.S. Food and Drug Administration

Jin Y. Jin, PhD
Genentech

Geoff Oxnard, MD
Loxo@Lilly

Alex Phipps, PhD
AstraZeneca

Lillian Siu, MD
Princess Margaret Cancer Center

Julia Maues
Patient Centered Dosing Initiative

Closing Session – Questions

1. What aspects of dosage optimization did this workshop clarify for you?

2. How will pre-market dosage optimization impact the patient experience? How can this be most effectively communicated?

3. How do we start to implement what we learned? What resources do we need to get started?

4. What are key remaining challenges to dosage optimization that oncology stakeholders need to address?

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