

# **Clinical Pharmacology Regulatory Sciences in Drug Development and Precision Medicine: Current Status and Emerging Trends**

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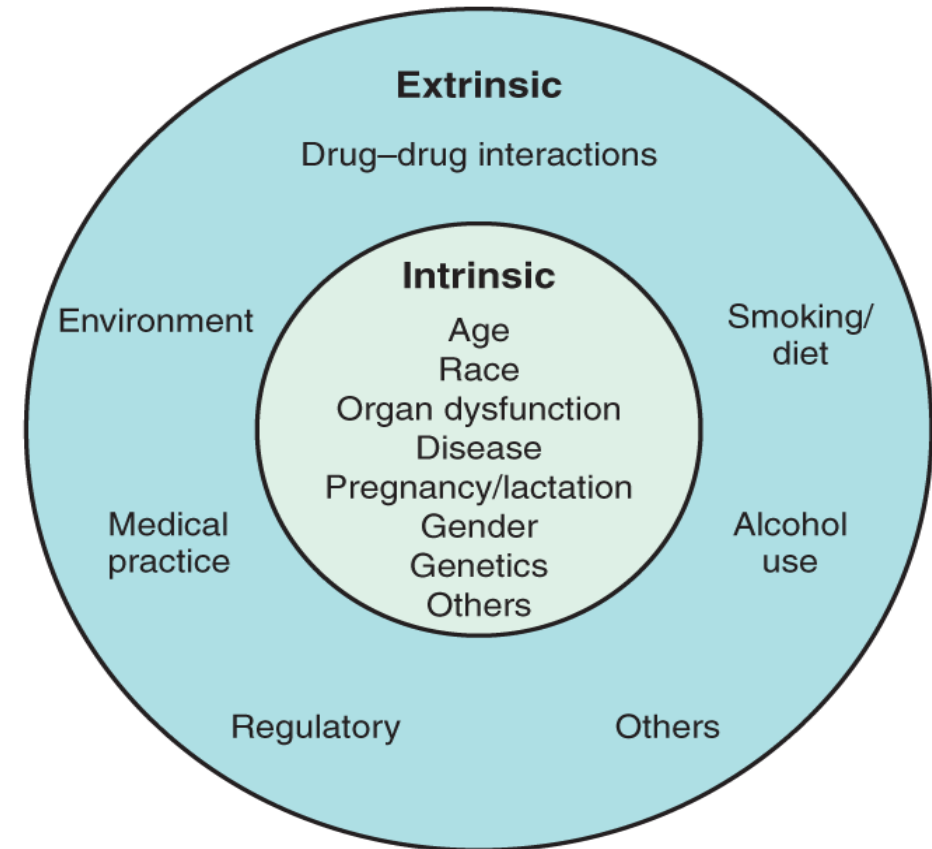
Regulatory Education for Industry (REdI) Conference for 2021

- Conflict of Interest: I have no competing interests for this work
- The views expressed are those of the author and do not reflect official policy of the FDA

# What is Clinical Pharmacology?



- The study of drugs in humans
- In the regulatory setting
  - Focusing on the impact of intrinsic and extrinsic factors on inter- and intra-patient variability in drug exposure and response
  - Contributing to the understanding of the benefit-risk profile in individuals and the development of therapeutic monitoring and management strategies
  - Playing a role in the development and qualification of drug development tools



PMID: 18714314

# Office of Clinical Pharmacology (OCP)

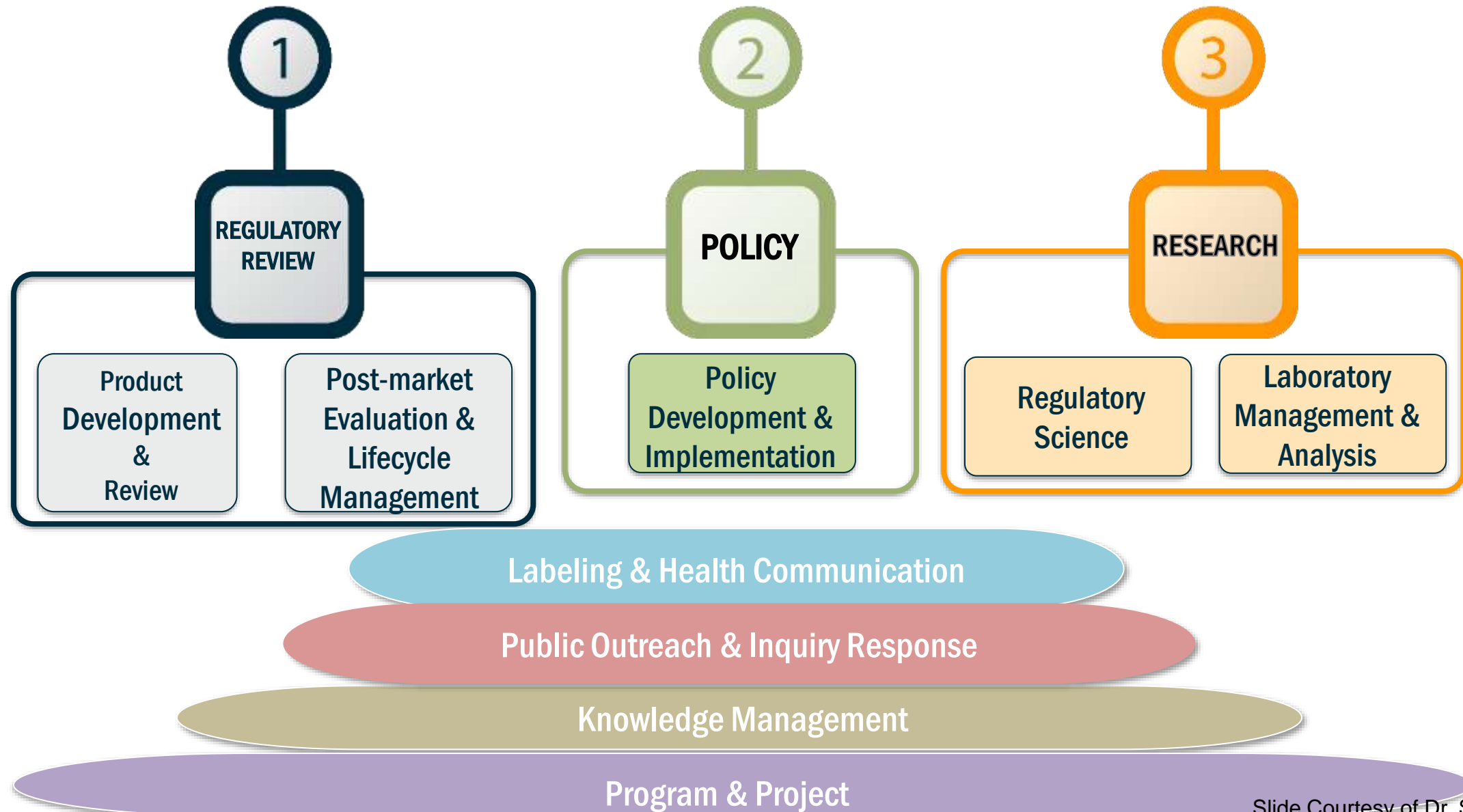
OCP is a dynamic, purpose-driven organization whose goals are to enhance drug development, promote regulatory science and innovation, and inform the optimal use of medications.

Improve public health by  
building and translating  
knowledge of drug  
response into  
patient-centered  
regulatory decisions of the  
highest quality



- Play a pivotal role in advancing development of innovative new medicines by applying state-of-the-art regulatory science and clinical pharmacology principles
- Promote therapeutic optimization and individualization through best practices in research, policy development, and drug evaluation throughout the product lifecycle

# OCP Core and Enabling Functions



# Clinical Pharmacology Studies During Drug Development

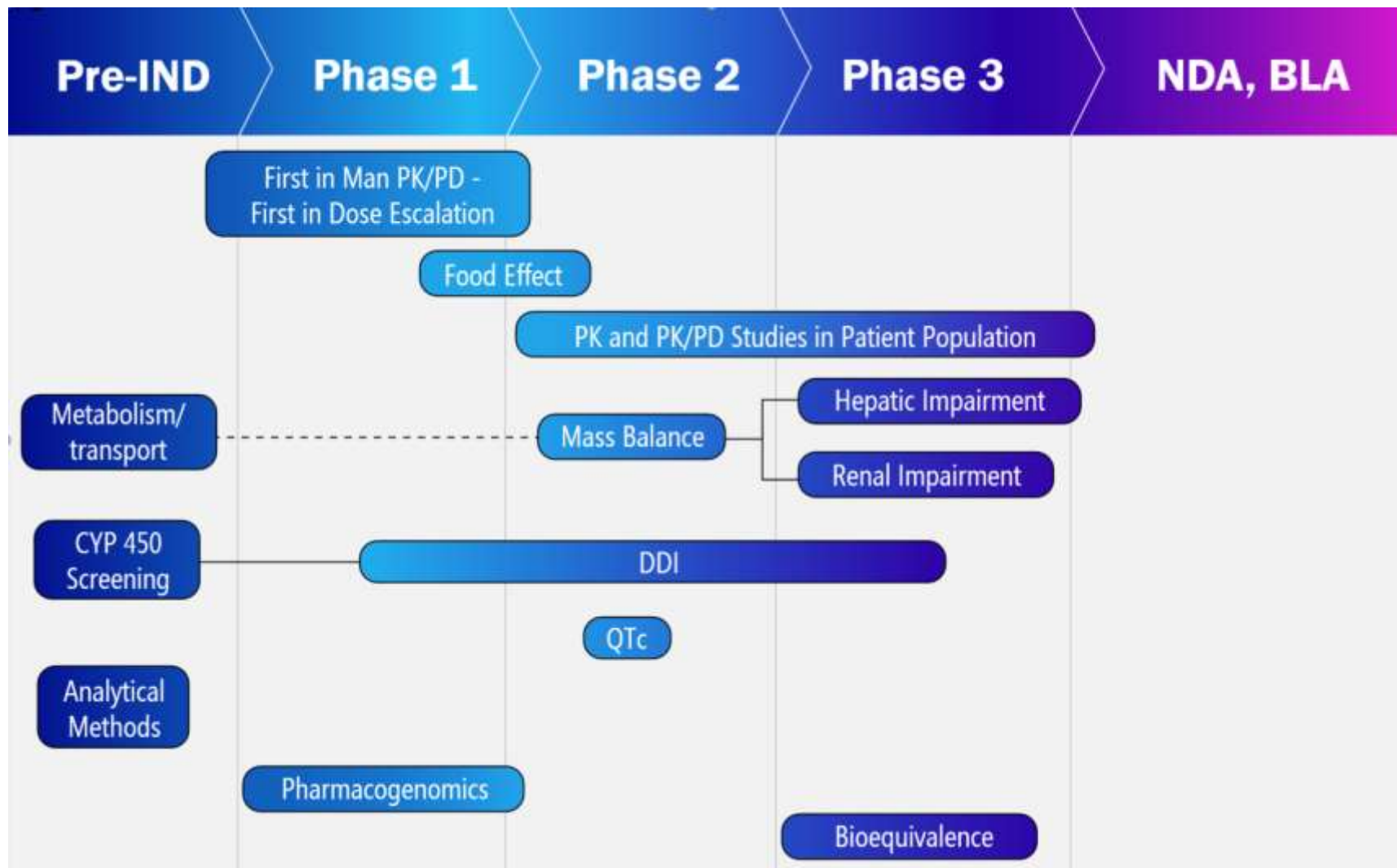
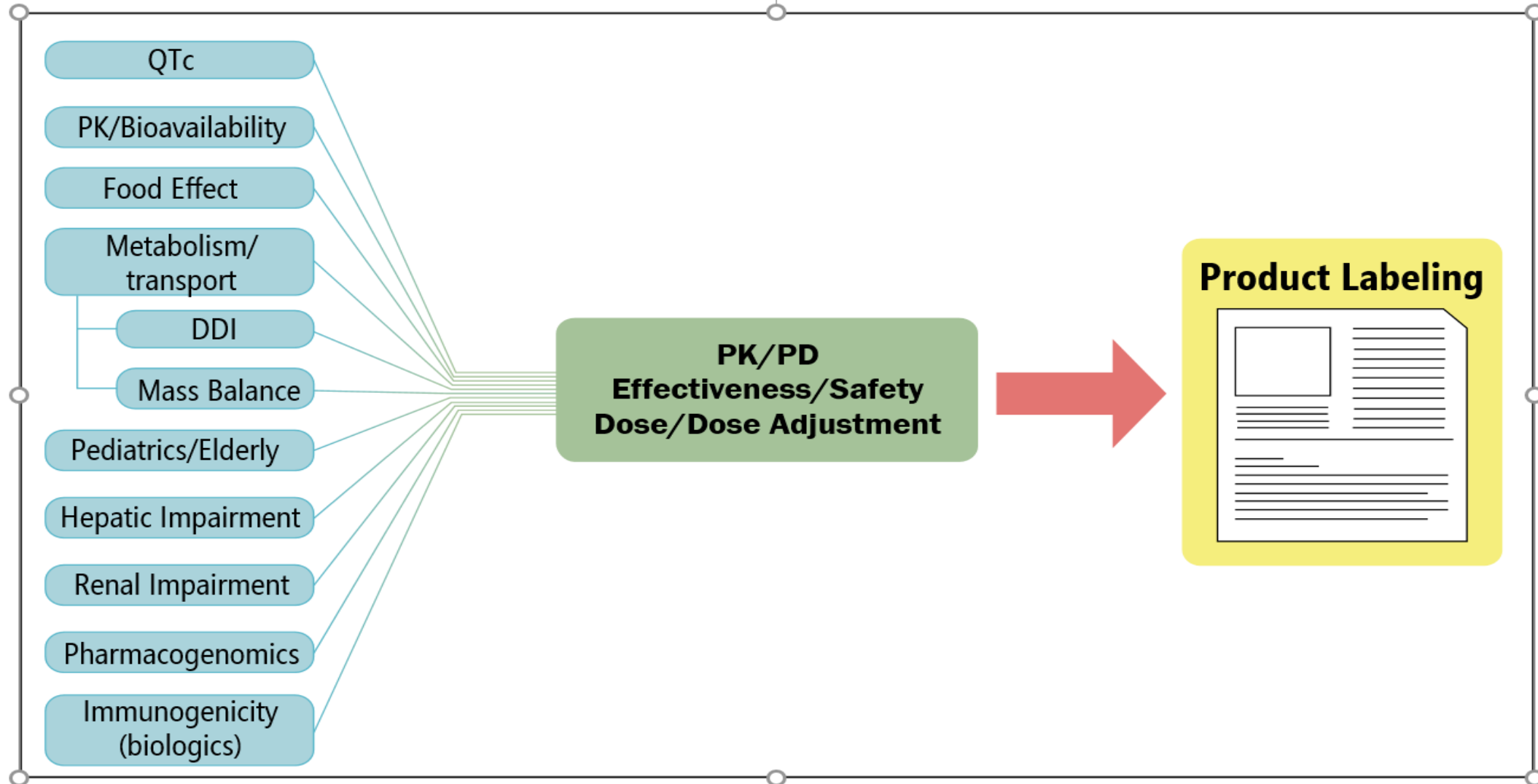


Figure created by Drs. Kimberly Bergman and Giang Ho

# Clinical Pharmacology Information in the Package Insert

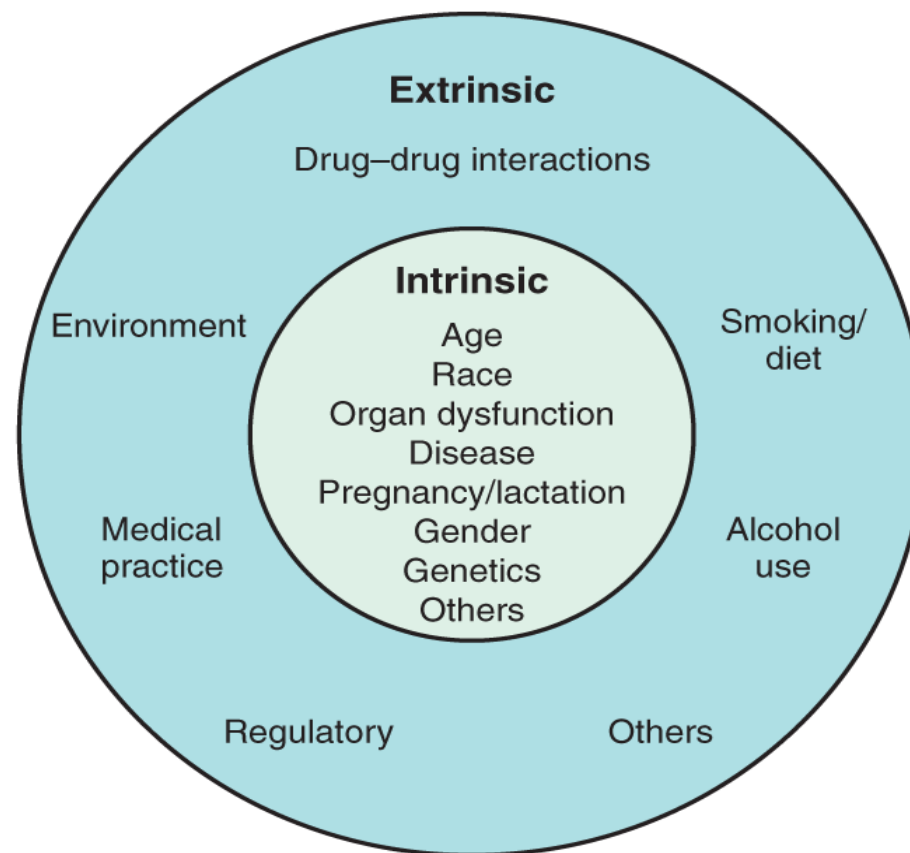


(PMID: [33846878](#))

## Take-Home Message #1



- Clinical Pharmacology is a critical component in drug development and precision medicine
  - the impact of intrinsic and extrinsic factors on inter- and intra-patient variability in drug exposure and response.
  - the benefit-risk profile in individuals
  - Appropriate dosing, therapeutic monitoring and management strategies





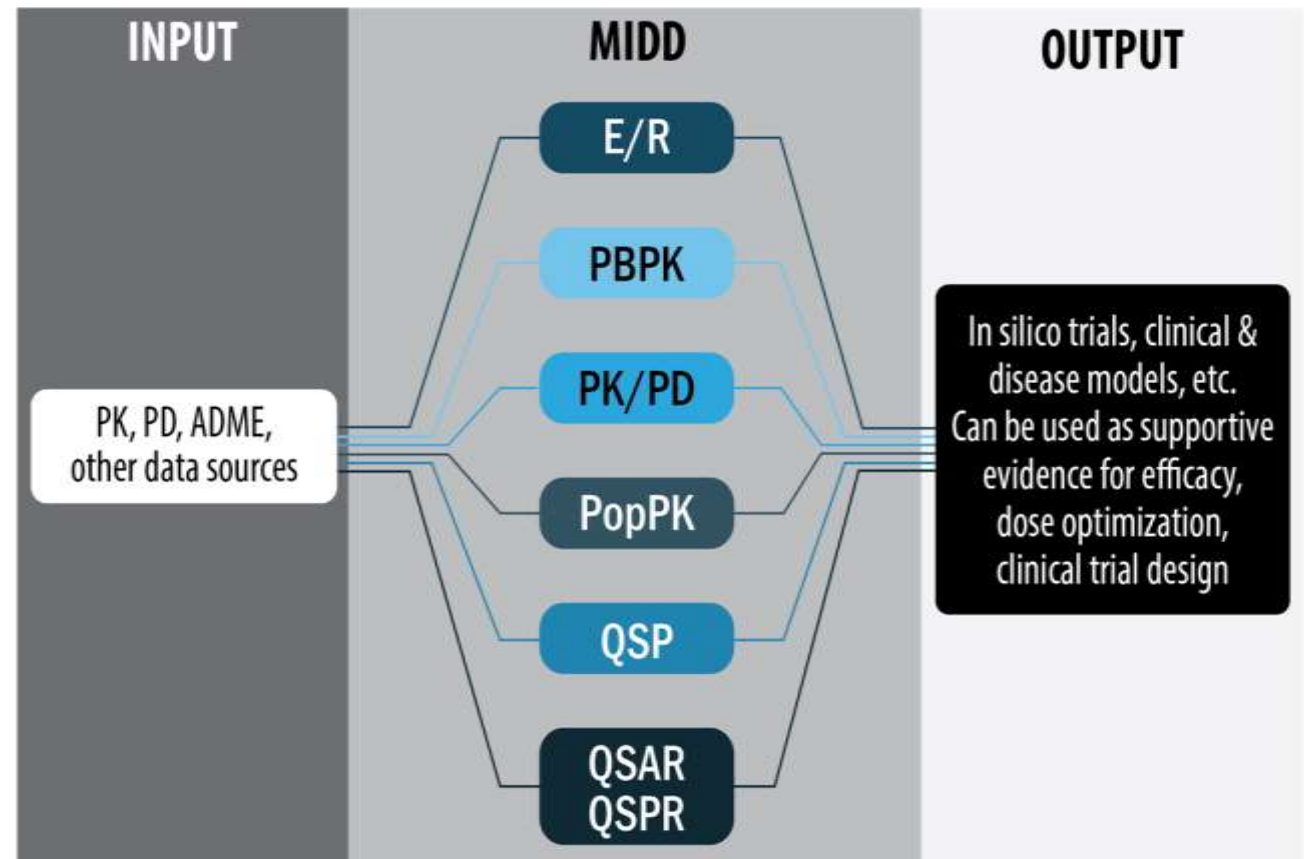
# Emerging Trends in Clinical Pharmacology Regulatory Sciences

- **The Model-Informed Drug Development (MIDD) Pilot Program**
- **The Use of Real-world Data (RWD) to Address Clinical Pharmacology Questions**
- **Leveraging Advances in Science into Tools for Drug development and Evaluation**



# What is Model-Informed Drug Development (MIDD)?

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

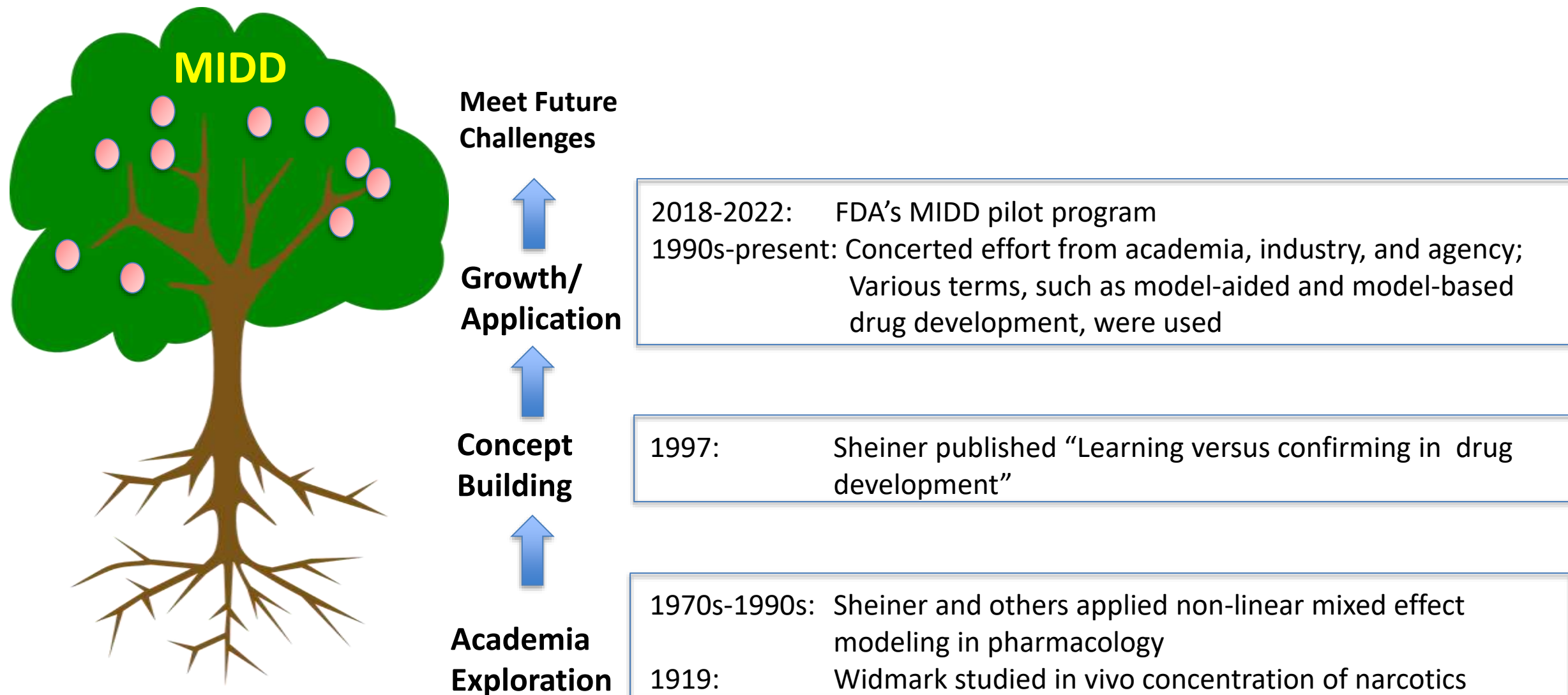


ADME: Absorption, Distribution, Metabolism, Excretion; PK/PD: Pharmacokinetic/Pharmacodynamic; QSAR: Quantitative Structure Activity Relationship; QSP: Quantitative Systems Pharmacology; QSPR: Quantitative Structure-Property Relationship

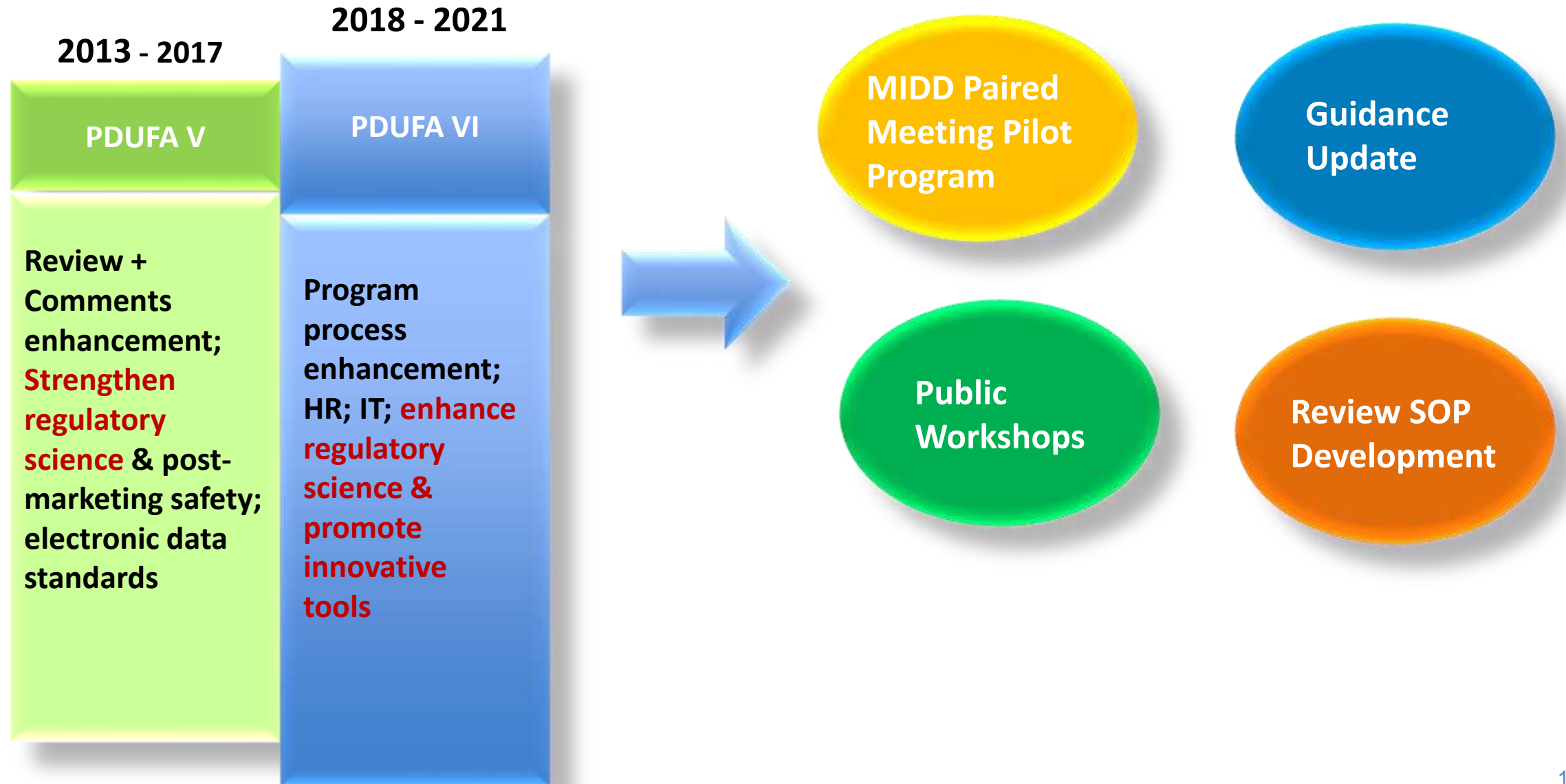
<https://www.federalregister.gov/documents/2018/04/17/2018-08010/pilot-meetings-program-for-model-informed-drug-development-approaches>

(PMID: [33846878](https://pubmed.ncbi.nlm.nih.gov/33846878/))

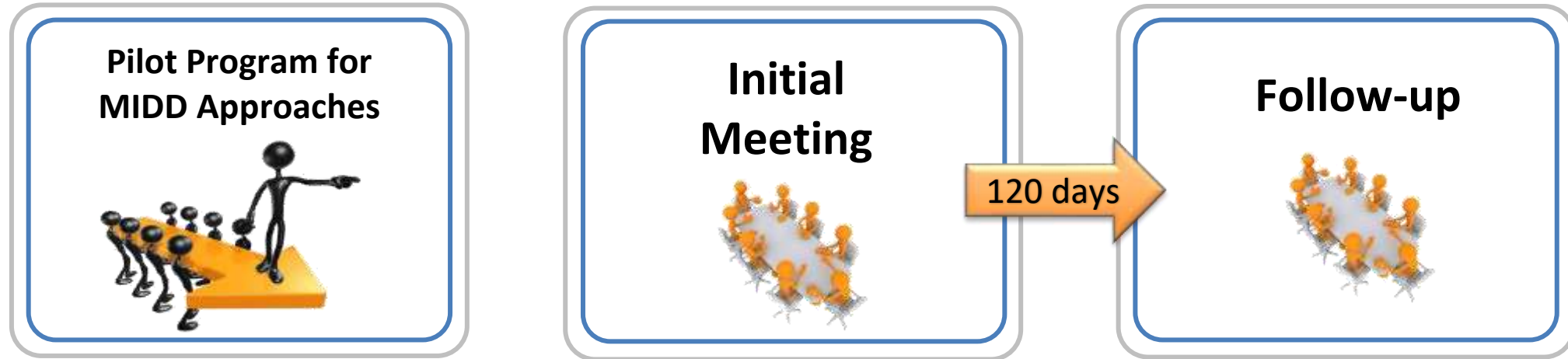
# MIDD as an Evolving Concept



# PDUFA VI Initiatives



- To promote early interaction between the drug developers and FDA on key issues.

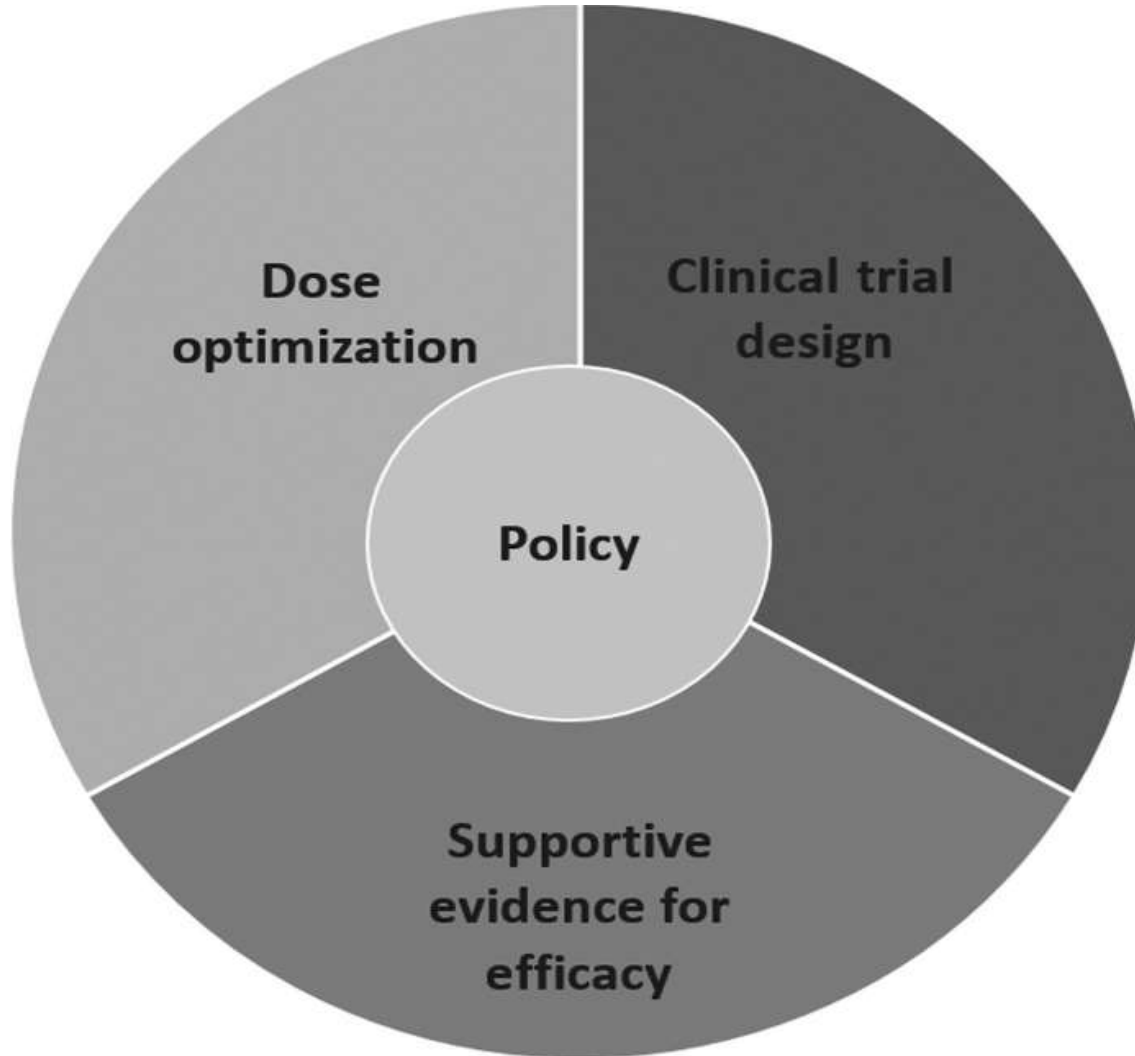


- Provides an opportunity for drug developers and FDA to discuss the application of MIDD approaches to the development and regulatory evaluation of medical products in development**

Slide courtesy of Dr. E. Ford

# MIDD as a Regulatory Tool

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# MIDD Case Study 1 - Sotalol

## Sotalol is an anti- arrhythmic drug



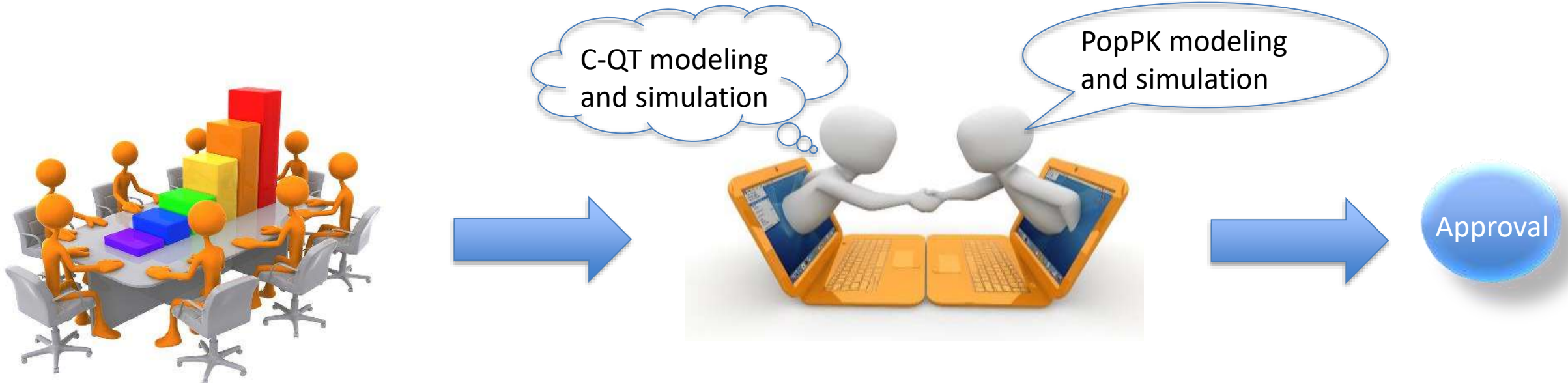
- Intensive QTc monitoring until steady state is achieved, during
  - Initiation of the treatment
  - Dose escalation.
- In hospital monitoring **for 3 days** is recommended.

# Sotalol Case



## IV Infusion to minimize hospital stay:

- Loading dose to reach steady state.
- Stress test to ensure safety.



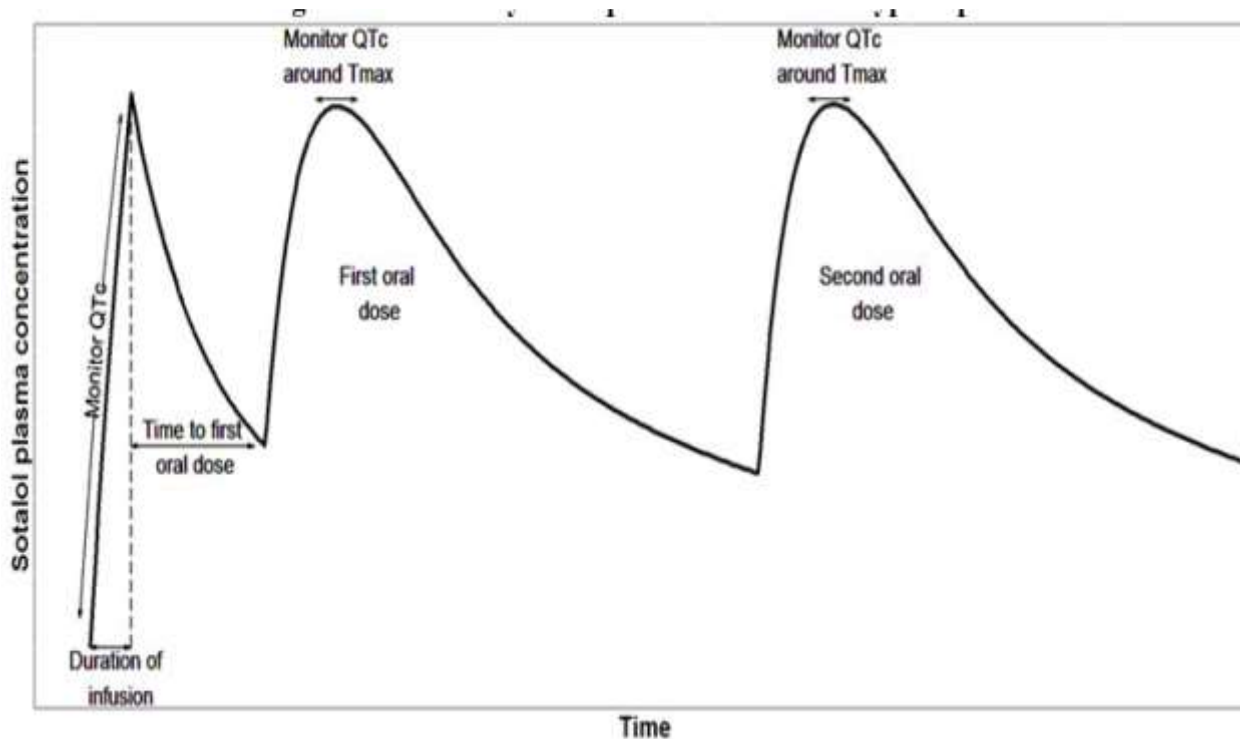
MIDD program allows granular discussion on modeling and simulation strategy to derive IV dosing under different scenarios

In-depth discussion on modeling & simulation results and recommendations during NDA review.



# Loading Dose Strategy

Computer-based simulations incorporating sotalol dose-exposure-QTc relationships were used to derive the intravenous loading doses.



- 1-hr IV infusion:
- Monitor QT every 15 minutes during infusion.
- Monitor QT around Tmax of the first dose (in all patients) and second oral dose (in patients with CrCL > 60 mL/min).
- Stopping/adjustment criteria (> 500ms or 20% increase from baseline) . To lower dose or discontinue the treatment.

# Recommended Dosing



Creatinine Clearance* [mL/min]	Intravenous loading dose [mg] to be administered over 1 hour when the oral dose is going from...				Minimum delay to first oral dose [hours]	Oral dosing interval [hours]
	Sotalol Initiation		Sotalol Escalation			
	0 to 80 mg**	0 to 120 mg	80 to 120 mg	120 to 160 mg		
>90	60	90	75	90	4	12
60-90	82.5	125	82.5	105	4	12
30-60	75	112.5	82.5	105	6	24
10-30	75	112.5	82.5	105	12	48

\*Calculated using Cockcroft Gault formula

\*\*Recommended starting dose

# MIDD Case Study 2 - Ramucirumab



Ramucirumab is a human VEGFR 2 antagonist indicated for the treatment of various cancers.

The originally approved dosing in patients is 8-10 mg/kg given as intravenous infusion over the time course of **1 hour**.

# Discussion under MIDD Program



## **MIDD Program:**

- To align objectives
- To understand the modeling approaches.
- To address other relevant issues in the development (e.g., potential safety related faster infusion rate – infusion rate reaction).
- To identify the data and approaches to move the development forward.



## **SBLA Submission:**

- Extensive discussion in understanding the data and modeling results.
- Collaboration further on the MIDD approaches on PK and safety information.

# Recommended Dosing Regimens

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Section 2 of Cryamza<sup>®</sup> label:

The recommended dosage of CYRAMZA is 8 mg/kg every 2 weeks administered by intravenous infusion over 60 minutes. If the first infusion is tolerated, all subsequent CYRAMZA infusions may be administered over 30 minutes. Continue CYRAMZA until disease progression or unacceptable toxicity.

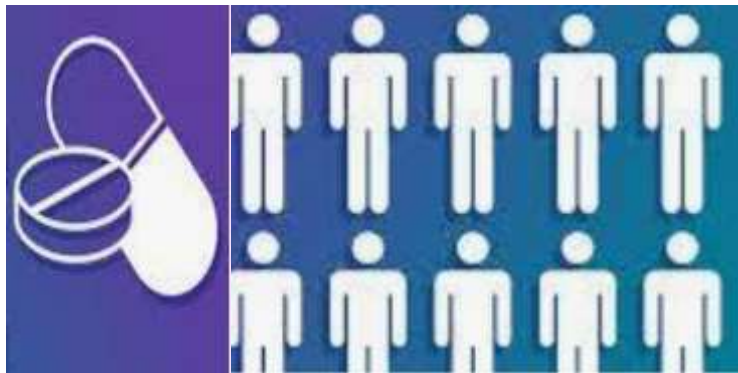
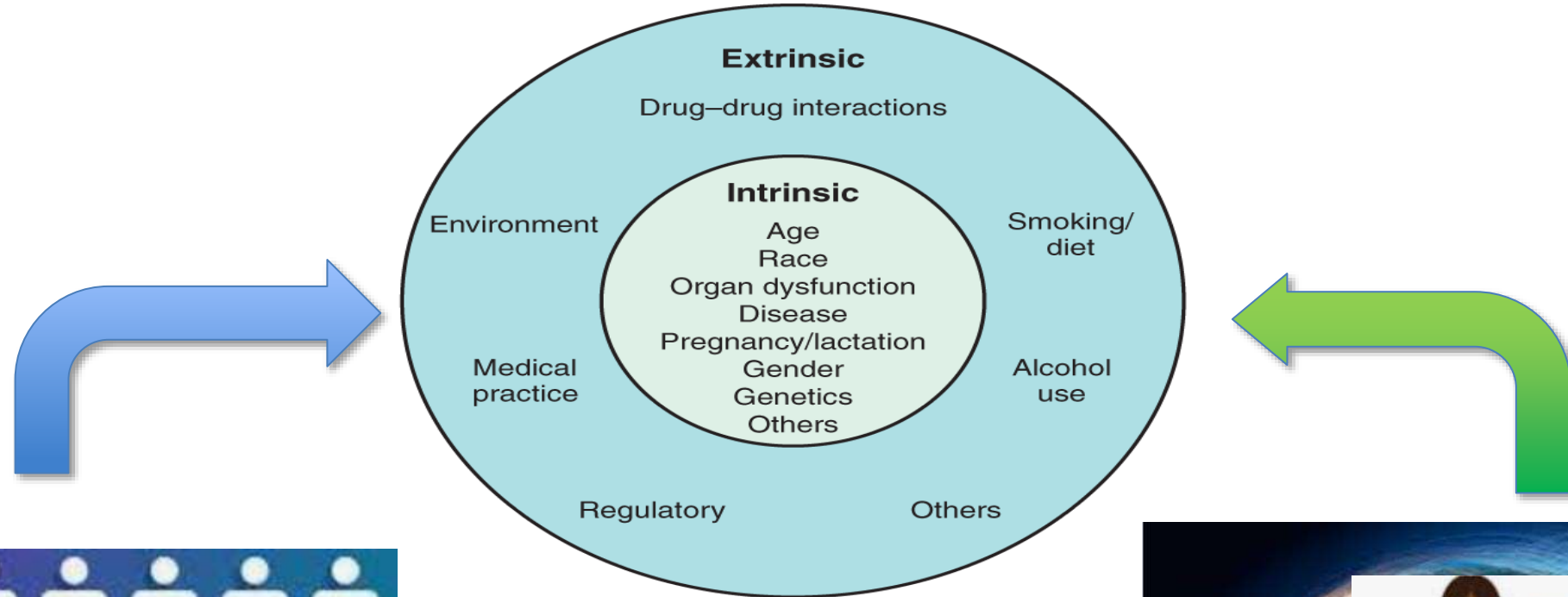
# Take-Home Message #2

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- MIDD can improve both efficiency and quality of drug development and precision medicine
  - saving cost/time
  - Improving patient care

# Can Real-World Data be Used to Address Clinical Pharmacology Questions?



Clinical Trials



RWD/E



# Real-World Data and Clinical Pharmacology



**Table 1 Selected literature examples of the utility of RWD to generate RWE**

Therapeutic product	Methods	Outcome and Impact	Limitations
RWE to optimize dose and dosing regimen			
Palbociclib <sup>3</sup>	A retrospective observational study of structured data from a US EMR database was used to understand the clinical and demographic characteristics of patients	This study demonstrated reasonable adherence to the recommended starting dose and monitoring patterns for palbociclib in a real-world	This study was based on structured EMR data only and did not include unstructured EMR data
Aspirin (NCT02697916)	ADAPTABLE (Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-Term Effectiveness; NCT02697916) is an open-label, randomized, parallel-	This study is reported to be currently enrolling by invitation. This is the first of such pragmatic trials to be conducted through PCORnet to help	
RWE for determining Impact of intrinsic and extrinsic factors			
Clopidogrel <sup>5,6</sup>	The authors <sup>5</sup> enrolled patients who received clopidogrel therapy and presented with an acute myocardial infarction in a nationwide French registry. They assessed	Simon et al. <sup>5</sup> concluded that patients with CYP2C19 loss-of-function alleles had a higher rate of subsequent cardiovascular events than those who	Given the observational nature of the study, the role for polymorphisms on other genes or role of drug
St. John's Wort <sup>8</sup>	Multiple case reports have highlighted reduced blood cyclosporine concentration. Unwanted pregnancies in women while using oral contraceptives and St. John's Wort have been reported.	Multiple regulatory agencies (US, UK, German, and Swedish authorities) had warned of therapeutic failure of select comedications when concomitantly taken with St. John's Wort.	

Liu, Ramamoorthy, Huang, *Clin Pharmacol Ther* 106: 67-71, July 2019

<https://ascpt.onlinelibrary.wiley.com/doi/pdf/10.1002/cpt.1413>



# Real-World Data (RWD) and Real-World Evidence (RWE)

**RWD** is the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources, such as:



Electronic health records



Claims and billing activities



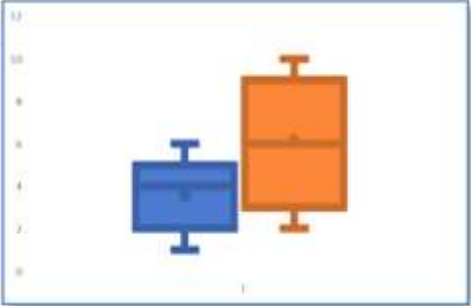
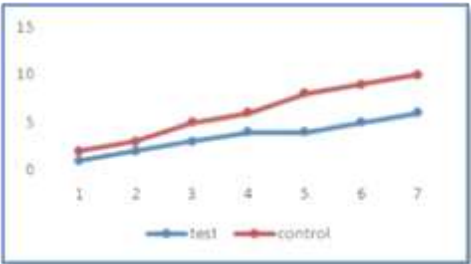
Product and disease registries



Patient-generated data including in home-use settings



**RWE** is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.



# Challenges with the Use of Real-World Data

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- Data quality and completeness
  - Many RWD sources were not built for research purpose
  - Various information for a patient may exist in different electronic systems that lack cross-communication
- Unstructured data
- Potential confounding and bias
  - Lack of randomization
- Need for common data platforms and data standards



- The research using RWD can be challenging
- Regulatory research is needed for us to learn where RWD can be helpful and to develop best practice

- **Case 1:** Renal/Hepatic Dysfunction and Clinical Outcomes in Cancer Patients Treated with Immune Checkpoint Inhibitors (ICI)
- **Case 2:** Pneumonitis Incidence in Patients with Non-Small Cell Lung Cancer Treated with Immunotherapy or Chemotherapy in Clinical Trials and RWD

Common characteristics of the 2 cases:

- Collaboration projects
- Both clinical trial data and RWD were analyzed
- Analyses protocol discussed and developed upfront
- **Generally consistent results from RWD and clinical trial data**

[https://ascopubs.org/doi/10.1200/JCO.2019.37.15\\_suppl.2569](https://ascopubs.org/doi/10.1200/JCO.2019.37.15_suppl.2569)

AACR annual meeting 2020; <https://www.ascopost.com/videos/aacr-virtual-annual-meeting-2020/qi-liu-on-pneumonitis-immunotherapy-and-chemotherapy-in-nscl/>

# Case Study: Pneumonitis Incidence in Patients with Non-Small Cell Lung Cancer Treated with Immunotherapy or Chemotherapy in Clinical Trials and RWD

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Qi Liu<sup>1</sup>, Chenan Zhang<sup>2</sup>, Yutao Gong<sup>1</sup>, Hao Zhu<sup>1</sup>, Elaine Chang<sup>1</sup>, Cheryl Cho-Phan<sup>2</sup>, Jonathan Hirsch<sup>2</sup>, Michael A. Thompson<sup>3</sup>, Gideon Blumenthal<sup>1\*</sup>, Shiew Mei Huang<sup>1</sup>, Thomas D. Brown<sup>2</sup>

1. US Food and Drug Administration, Silver Spring, MD
2. Syapse, San Francisco, CA
3. Advocate Aurora Health, Milwaukee, WI

[AACR 2020; https://www.ascopost.com/videos/aacr-virtual-annual-meeting-2020/qi-liu-on-pneumonitis-immunotherapy-and-chemotherapy-in-nsclc/](https://www.ascopost.com/videos/aacr-virtual-annual-meeting-2020/qi-liu-on-pneumonitis-immunotherapy-and-chemotherapy-in-nsclc/)

To evaluate treatment-associated pneumonitis (TAP) in patients with advanced NSCLC

- Using data from clinical trials and real world data (RWD)
- Treated with ICI or chemotherapies
- With and without past medical history (PMH) of pneumonitis

# Conclusion



- Higher TAP incidence among ICI-treated NSCLC patients compared to those receiving chemotherapy alone
- Consistent numerical increase in TAP with PMH of pneumonitis
  - In both ICI and chemotherapy treated groups
  - In both clinical trials and RWD

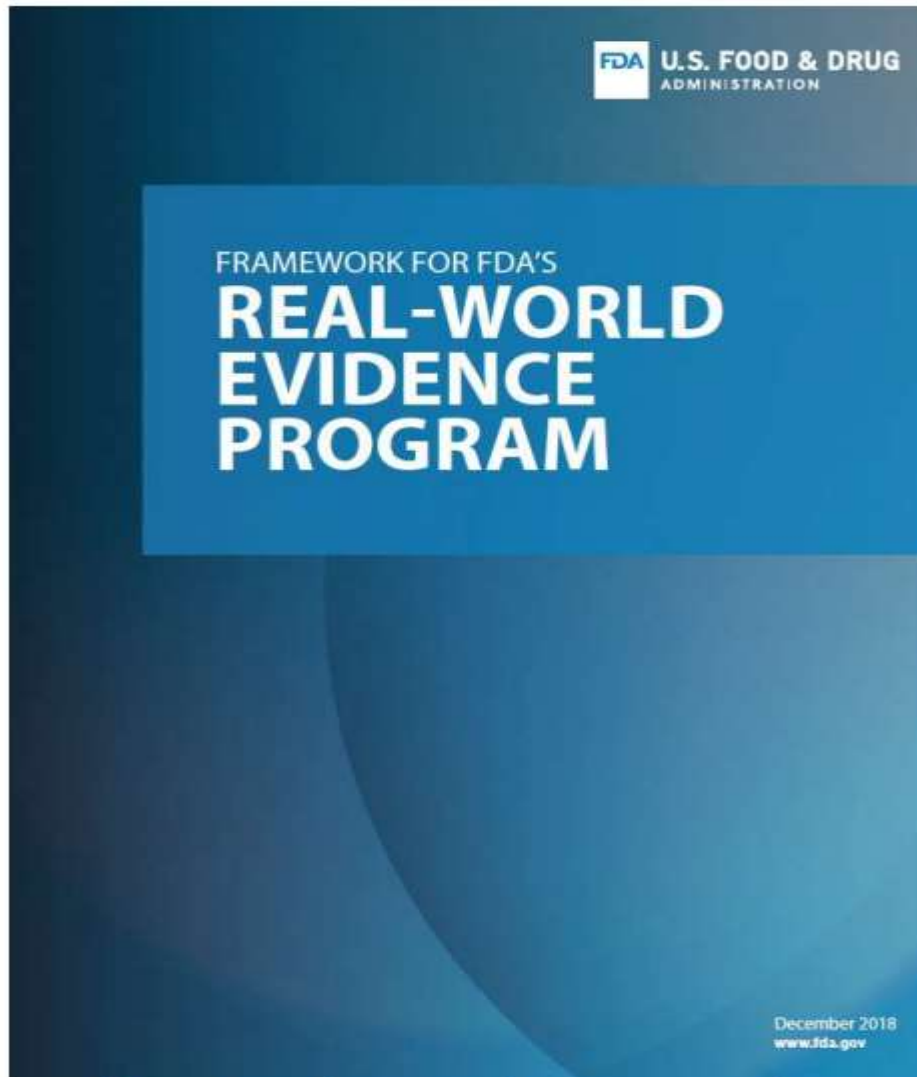
Incidence of TAP point estimate (95% confidence interval)			
Clinical Trials (N=6491)		RWD (N=1262)	
ICI +/- chemotherapy (N=3723)	chemotherapies (N=2768)	ICI +/- chemotherapy (N=615)	chemotherapies (N= 647)
169/3723 4.5% (3.9-5.3%)	29/2768 1.0% (0.7-1.5%)	20/615 3.3% (2.1-5.0%)	15/647 2.3% (1.4-3.8%)

Incidence of TAP point estimate (95% confidence interval)				
PMH of Pn	Clinical Trials		RWD	
	ICI +/- chemotherapy (N=3723)	chemotherapies (N=2768)	ICI +/- chemotherapy (N=615)	chemotherapies (N= 647)
Yes CT N=48 RWD N=33	5/30 16.7% (7.3-33.6%)	2/18 11.1% (3.1-32.8%)	3/21 14.3% (5.0-34.6%)	1/12 8.3% (0.4-35.4%)
No CT N=6443 RWD N=1229	164/3693 4.4% (3.8-5.2%)	27/2750 1.0% (0.7-1.4%)	17/594 2.9% (1.8-4.5%)	14/635 2.2% (1.3-3.7%)

## Limitation

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- Small subgroups ( $\leq 30$  patients) for those with PMH of pneumonitis
- Relatively small numbers of TAP in RWD cohorts
- Variable follow-up duration
- Generalizability from one Health System to others



- **Data:** Is the RWD fit for use?
- **Design:** Can the trial or study design used to generate RWE provide adequate scientific evidence to answer or help answer the regulatory question?
- **Conduct:** Does the study conduct meet FDA regulatory requirements?

<https://www.fda.gov/media/120060/download>



## Take-Home Message #3

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- RWD can be used to address clinical pharmacology questions.
  - There are challenges in the application.
  - More research needs to be conducted to learn where RWD can be helpful and to develop best practice.

# Leveraging Advances in Science into Tools for Drug development and Evaluation



## FDA/CDER Microphysiological Systems Laboratory

Review | Open Access |

### Liver Microphysiological Systems for Predicting and Evaluating Drug Effects

Alexandre J. S. Ribeiro , Xinning Yang, Vikram Patel, Rajnikanth Madabushi, David G. Strauss

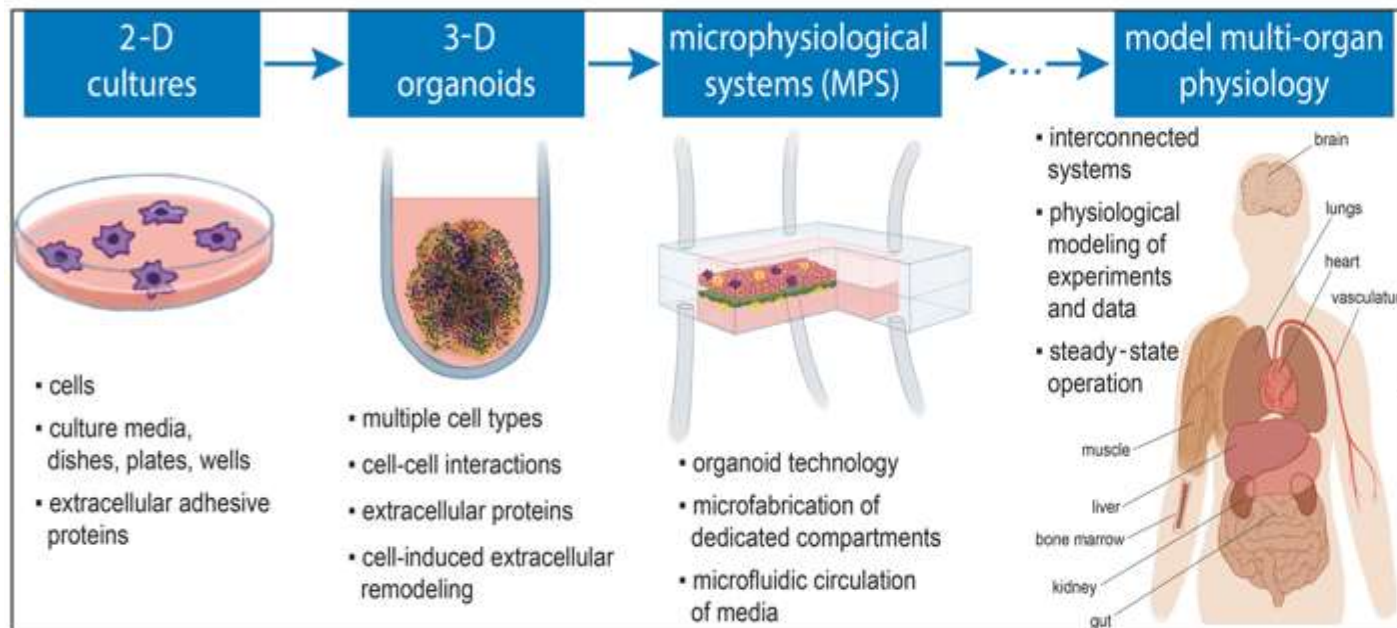
[\*Clinical Pharmacology & Therapeutics\* 2019;106:139-47.](#)

ARTICLE | Open Access |

### Characterizing the Reproducibility in Using a Liver Microphysiological System for Assaying Drug Toxicity, Metabolism and Accumulation

Andres Rubiano, Amruta Indapurkar, Ryosuke Yokosawa, Alina Miedzik, Barry Rosenzweig, Ayesha Arefin, Chloe M. Moulin, Keri Dame, Neil Hartman, Donna A. Volpe, Murali K. Matta, David J. Hughes, David G. Strauss, Tomasz Kostrzewski, Alexandre J.S. Ribeiro

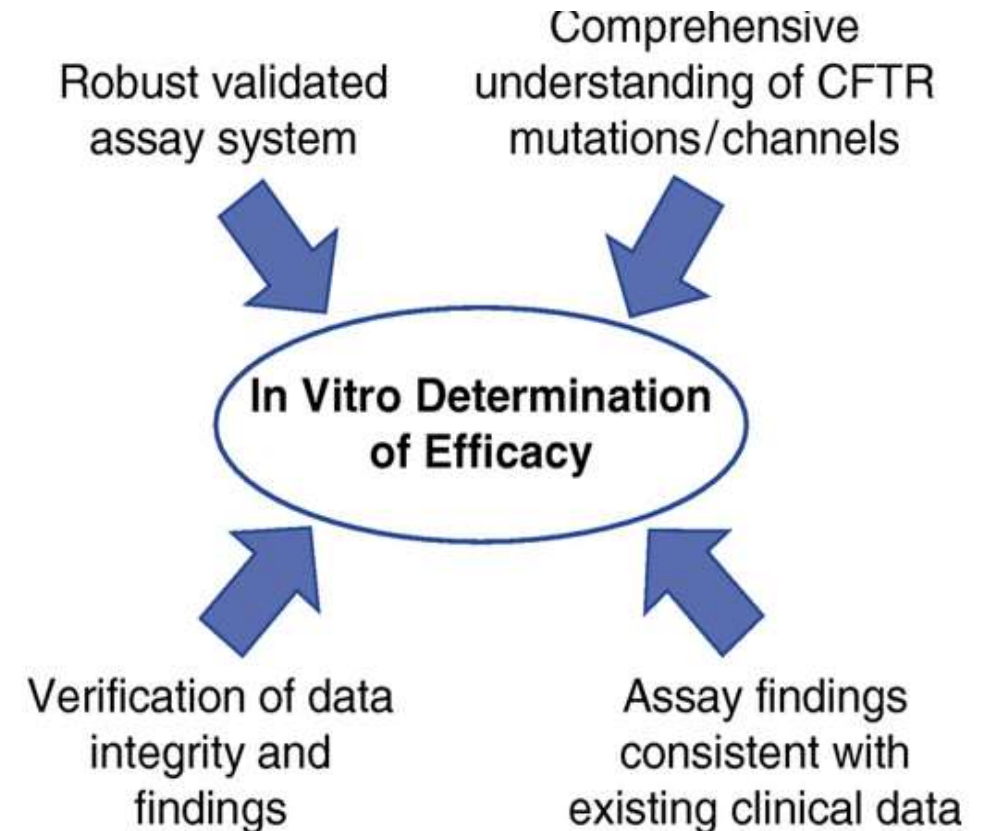
[\*Clinical & Translational Science\* 2020 \[epub\].](#)



# In Vitro Pharmacology Assays for Precision Medicine

*An in vitro* approach to determine the efficacy of ivacaftor in the treatment of cystic fibrosis (CF)

- Ivacaftor is indicated for the treatment of CF in patients age 4 months and older who have one mutation in the CFTR gene that is responsive to ivacaftor based on clinical and/or in vitro assay data.



(PMID: 29020455)

## Take-Home Message #4

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- Clinical Pharmacology can leverage advances in science into useful tools for drug development and evaluation
  - Improve the efficiency and quality of drug development
  - Advance precision medicine

1. Clinical Pharmacology is a critical component in drug development and precision medicine
2. MIDD can improve both efficiency and quality of drug development and precision medicine
3. RWD can be used to address clinical pharmacology questions
4. Clinical Pharmacology can leverage advances in science into useful tools for drug development and evaluation

## Conclusion

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- Continued advances in clinical pharmacology can be the basis of
  - more rational and efficient drug development
  - More precise treatment to the patients for better efficacy and safety
- FDA is strongly committed to working with all stakeholders to further the ever-expanding discipline of clinical pharmacology to promote public health



# Acknowledgement

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