Making Modeling & Simulation an Everyday Habit in Your Organization

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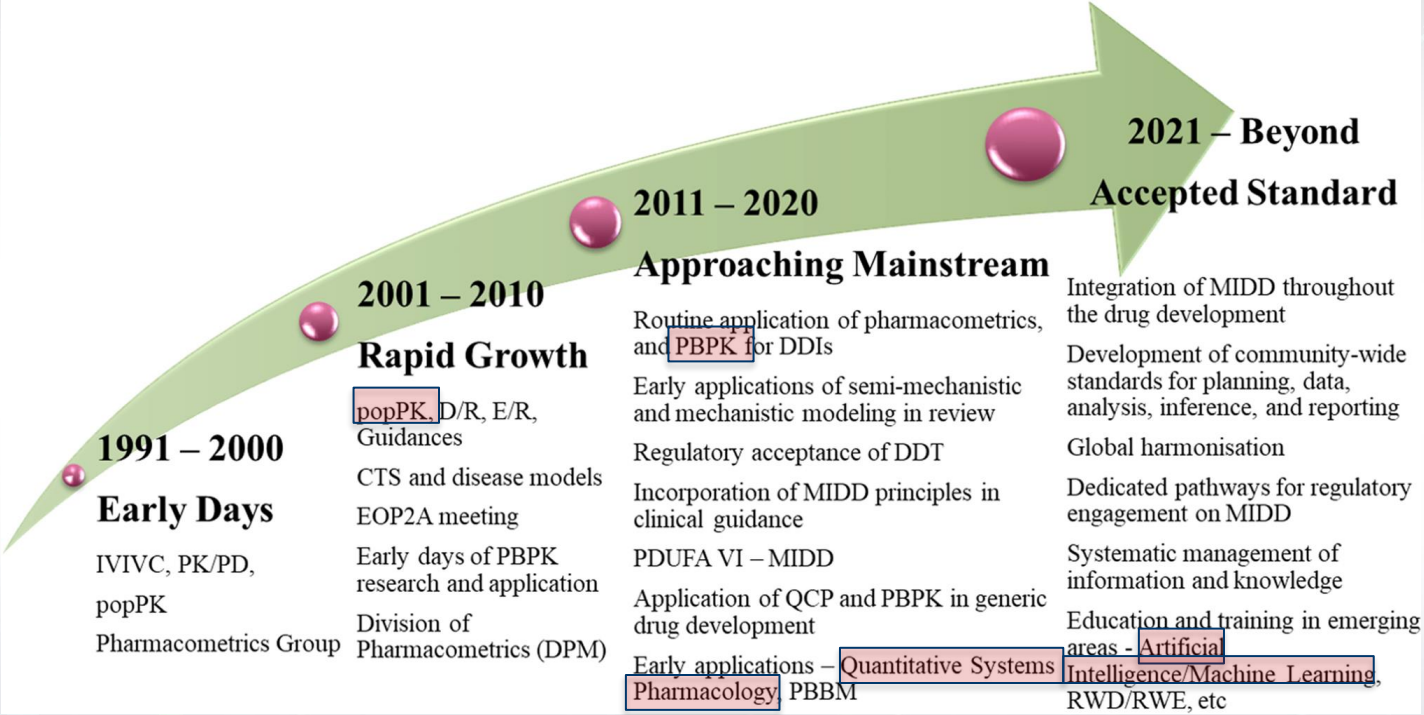
Director, Learning Services

SimulationsPlus MIDD+ Model Informed Drug Development + 2023

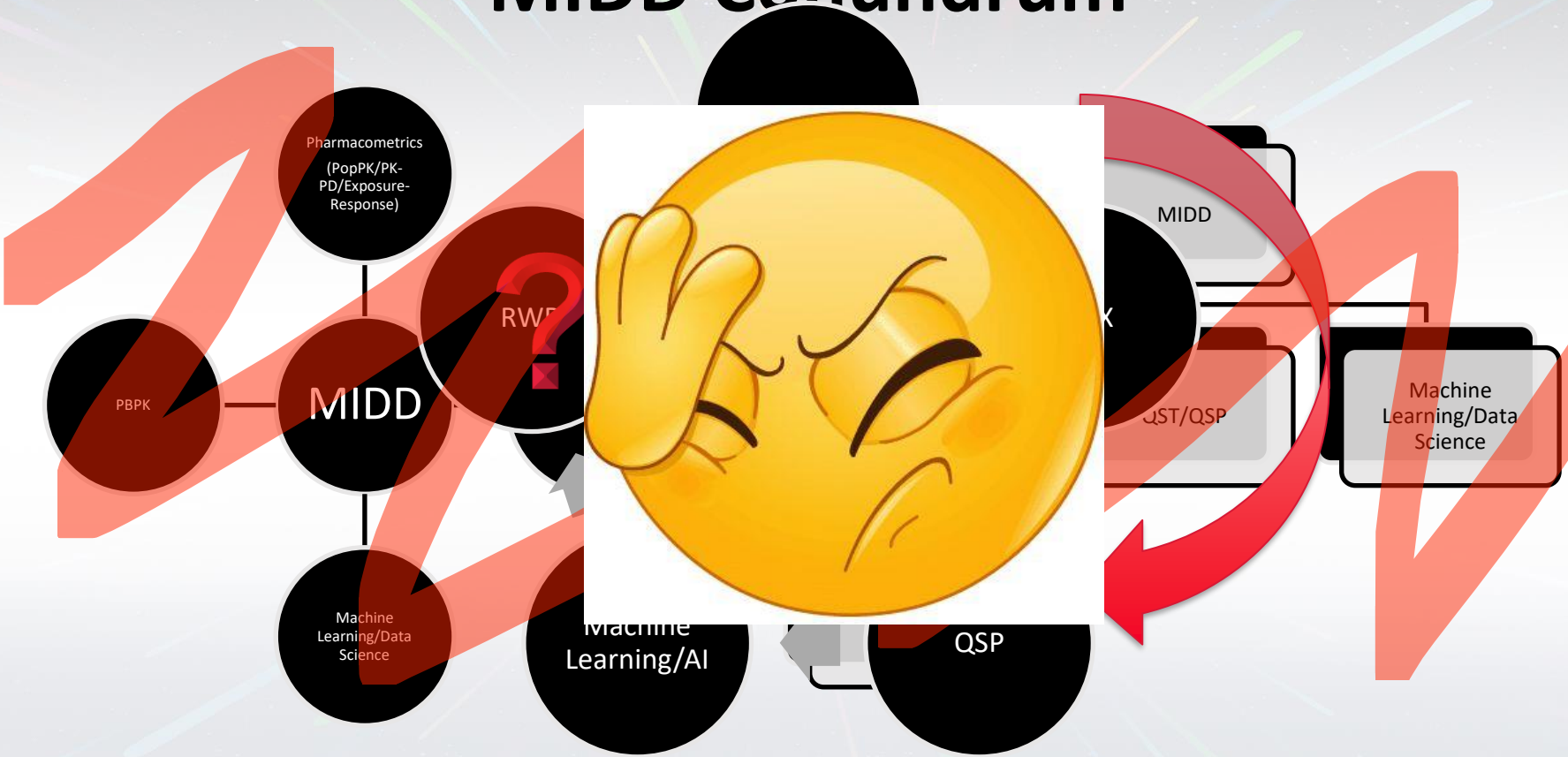
SimulationsPlus

History of MIDD



Madabushi, R., Seo, P., Zhao, L. *et al.* Review: Role of Model-Informed Drug Development Approaches in the Lifecycle of Drug Development and Regulatory Decision-Making. *Pharm Res* **39**, 1669–1680 (2022). https://doi.org/10.1007/s11095-022-03288-w

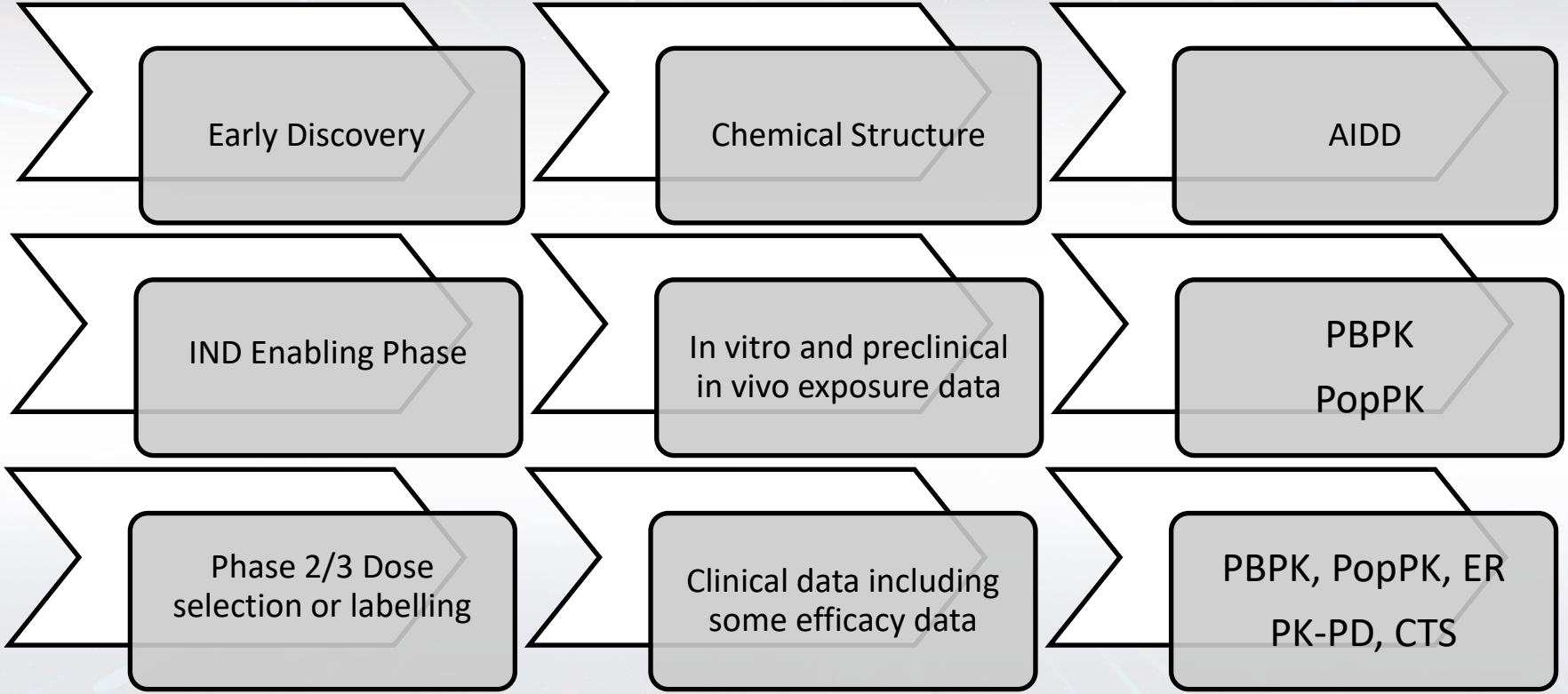
MIDD Conundrum



So how do we make it all make sense?

- 4 questions to ALWAYS ask in order to answer your final question
  - What?
  - Why?
  - How?
  - When?
- If you can answer these questions is should help you to determine the best approach to use

WHAT: What Data do you have available?



WHY: Why are we interested in building a model?

Untested Scenarios

Labelling Updates

FIH prediction

Special populations

DDI assessment

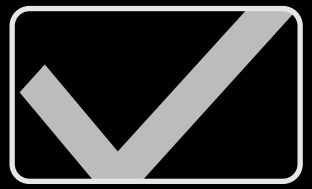
Food Effect

Formulation optimization

Bioequivalence Assessment

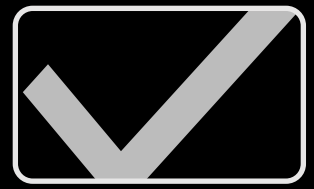
...

HOW: How will this model be used?



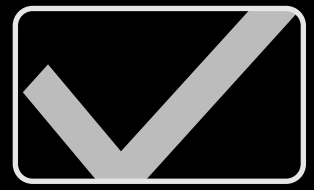
Regulatory Submission

- Less risk tolerant
- Greater scrutiny



Internal Decision Making

- More risk tolerant
- Use whatever tools needed to formulate a path moving forward (might be multifaceted)



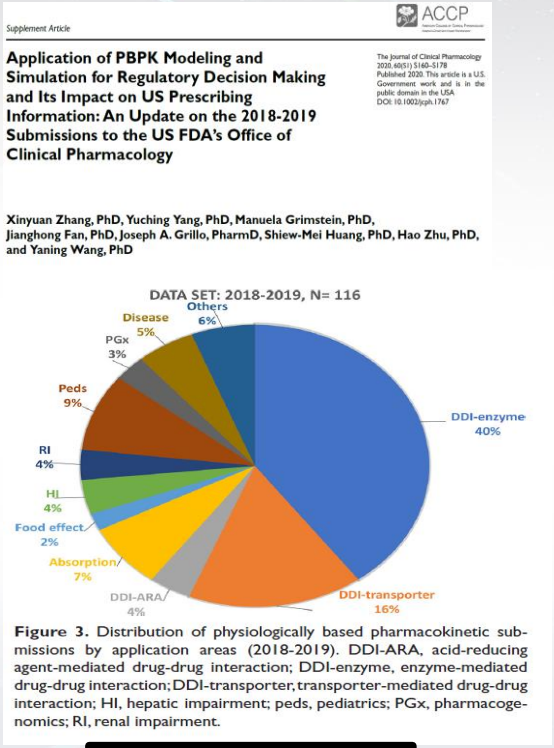
Innovation

- Willing to take optimal risk
- Want to make a difference
- Challenge status quo

How will this model be used?

Regulatory Submission

HOW: How will this model be used?



Supplement Article

ACCP

Application of PBPK Modeling and Simulation for Regulatory Decision Making and Its Impact on US Prescribing Information: An Update on the 2018-2019 Submissions to the US FDA's Office of Clinical Pharmacology

The Journal of Clinical Pharmacology 2020;60(S1):S160–S178
Published 2020. This article is a U.S. Government work and is in the public domain in the USA.
DOI: 10.1002/jcph.1767

Xinyuan Zhang, PhD, Yuching Yang, PhD, Manuela Grimstein, PhD, Jianghong Fan, PhD, Joseph A. Grillo, PharmD, Shiew-Mei Huang, PhD, Hao Zhu, PhD, and Yaning Wang, PhD

Figure 3. Distribution of physiologically based pharmacokinetic submissions by application areas (2018-2019). DDI-ARA, acid-reducing agent-mediated drug-drug interaction; DDI-enzyme, enzyme-mediated drug-drug interaction; DDI-transporter, transporter-mediated drug-drug interaction; HI, hepatic impairment; peds, pediatrics; PGx, pharmacogenomics; RI, renal impairment.

Zhang et al. J Clin Pharm 2020

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 December 2018
EMA/CHMP/458101/2016
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation

Draft agreed by Modelling and Simulation Working Group	April 2016
Draft agreed by Pharmacokinetics Working Party	May 2016
Adopted by CHMP for release for consultation	21 July 2016
Start of public consultation	29 July 2016
End of consultation (deadline for comments)	31 January 2017
Agreed by Modelling and Simulation Working Group	October 2018
Agreed by Pharmacokinetics Working Party	October 2018
Adopted by CHMP	13 December 2018
Date of coming into effect	1 July 2019

nload

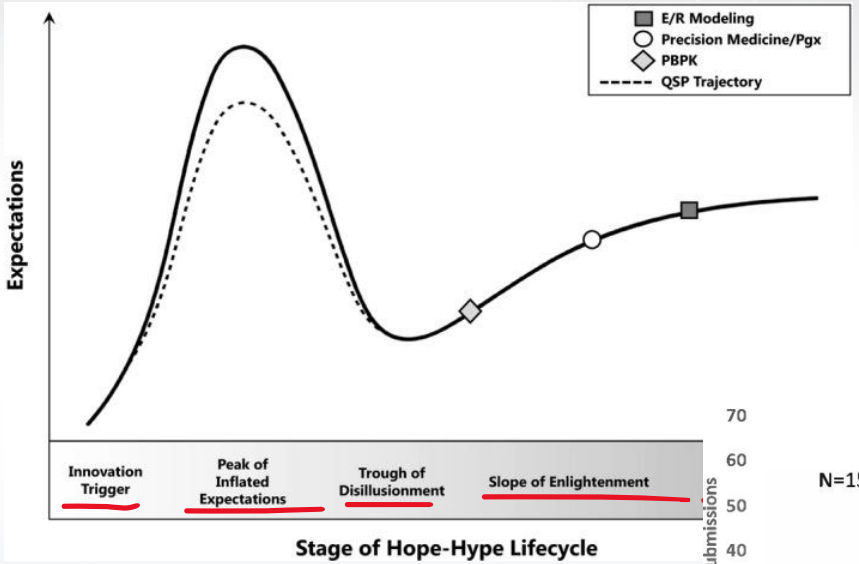
https://www.fda.gov/media/142500/download

NOV 2020

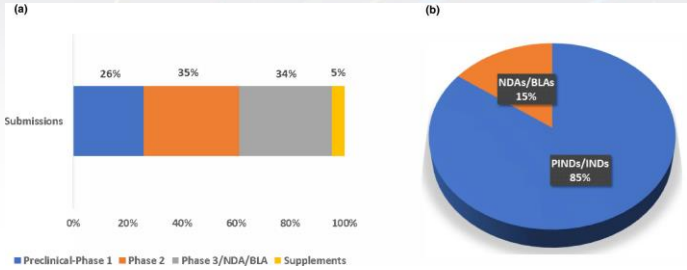
How will this model be used?

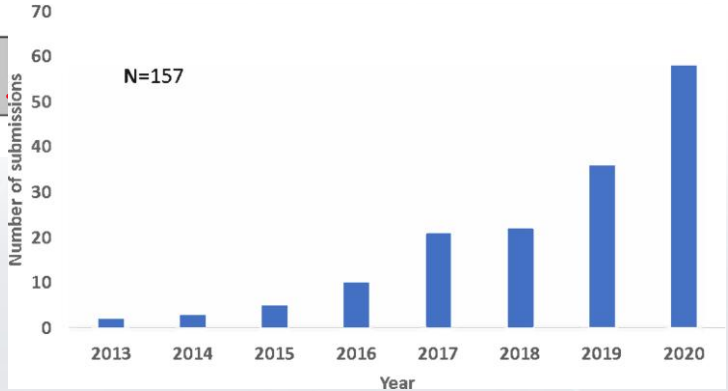
Internal Decision Making

HOW: How will this model be used?, cont'd



Zineh I. Quantitative Systems Pharmacology: A Regulatory Perspective on Translation. *CPT Pharmacometrics Syst Pharmacol*. 2019;8(6):336-339. doi:10.1002/psp4.12403





Bai JPF, Earp JC, Florian J, et al. Quantitative systems pharmacology: Landscape analysis of regulatory submissions to the US Food and Drug Administration. *CPT Pharmacometrics Syst Pharmacol*. 2021;10(12):1479-1484. doi:10.1002/psp4.12709

How will this model be used?

Innovation

HOW: How will this model be used?, cont'd

Clinical variance in CAR-T pharmacology deconvoluted using a mathematical model of T cell regulatory control

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dose escalation of Abecma in multiple myeloma.

Conclusions: To understand the drivers of exposure and response to CAR-T cell therapy we used a combination of mathematical modelling, bioinformatics, and machine learning to integrate disparate clinical datasets. Our QSP model predicts that memory cell turnover and cytotoxic potential are cell-intrinsic drivers of response, confirmed by bulk and single-cell RNA sequencing. Our machine learning classifier accurately predicts outcomes from pre-infusion transcriptomes, suggesting that CAR-T efficacy is primarily cell product intrinsic. Additional pharmacological variance predictively arises from cellular interactions with patient tumors.

Objectives:

Although machine learning (ML) has been identified as a powerful tool in many areas of drug development

Application of Artificial Intelligence & Machine Learning for Precision Medicine

The U.S. Food and Drug Administration (FDA) – in collaboration with the University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI) – will host a one-day virtual public workshop entitled "Application of Artificial Intelligence and Machine Learning for Precision Medicine" on **Friday, February 17, 2023**.

The purpose of this workshop is to review current methodologies, opportunities, challenges, and best practices to address the rapidly changing landscape of artificial intelligence and machine learning in the setting of drug development and precision medicine.

of Covariates in Population Models Empowered by Machine Learning." Journal of Pharmacokinetics and Pharmacodynamics, 2021. https://doi.org/10.1007/s10928-021-09757-w.

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r for Translational Medicine University of Maryland Baltimore

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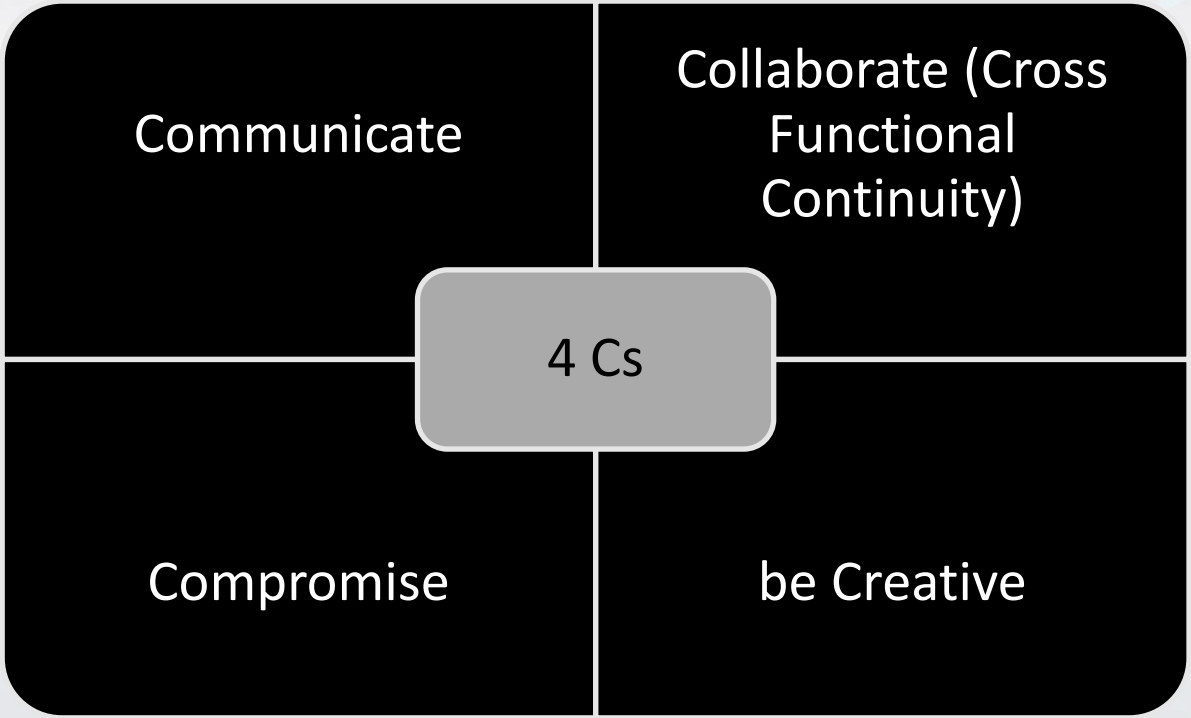
HOW: How will this model be used?, cont'd

ADMET Predictor® is a machine learning software tool that quickly and accurately predicts over 175 properties, including solubility, logP, pKa, and sites of CYP metabolism, integrating market-leading ADMET modeling with compound design, data analysis, SAR, and cheminformatics capabilities to support scientists across computational chemistry, medicinal chemistry, DMPK, and other disciplines

WHEN: When do you need to results by?

- Two weeks?
- One to two months?
- Six months?
- A year from now?

Tips for Successful Implementation of MIDD Approaches



Thank You!