

PBPK in Drug Development and Regulatory Decision-Making: Past, Present, and Future

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ACoP PBPK SIG Lunch

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The Journey of PBPK M&S Applications in Drug Development and Regulatory Submissions

DRUG DEVELOPMENT PRE-2008 | **REGULATORY USE 2008–2014** | **EXPANSION 2016–2020** | **HARMONIZATION 2022–2024**

2000

FDA guidance (2000)

Waiver of In Vivo BA/BE Studies for Immediate Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System

Pre-2008

Early drug development

- Candidate selection and
- optimization
- Human PK prediction from
- preclinical data
- Oral absorption and food-effect assessment

2008

Early capability

Dedicated staff and early PBPK submissions.

2012–2014

Initial regulatory use

Pediatric development, DDI evaluation, dose selection and PBPK reporting.

2016–2018

Guidance expansion

FDA and EMA guidance on DDI evaluation, PBPK qualification and reporting.

2019

Best practices

FDA workshop on PBPK for clinical pharmacology regulatory decisions.

2020

Biopharmaceutics applications

- FDA draft guidance on oral drug products and manufacturing changes.
- ICH M9 BCS based biowaivers

2022–2024

ICH harmonization

2022: ICH M12 draft DDI guidance

2024: ICH M15 draft MIDD principles

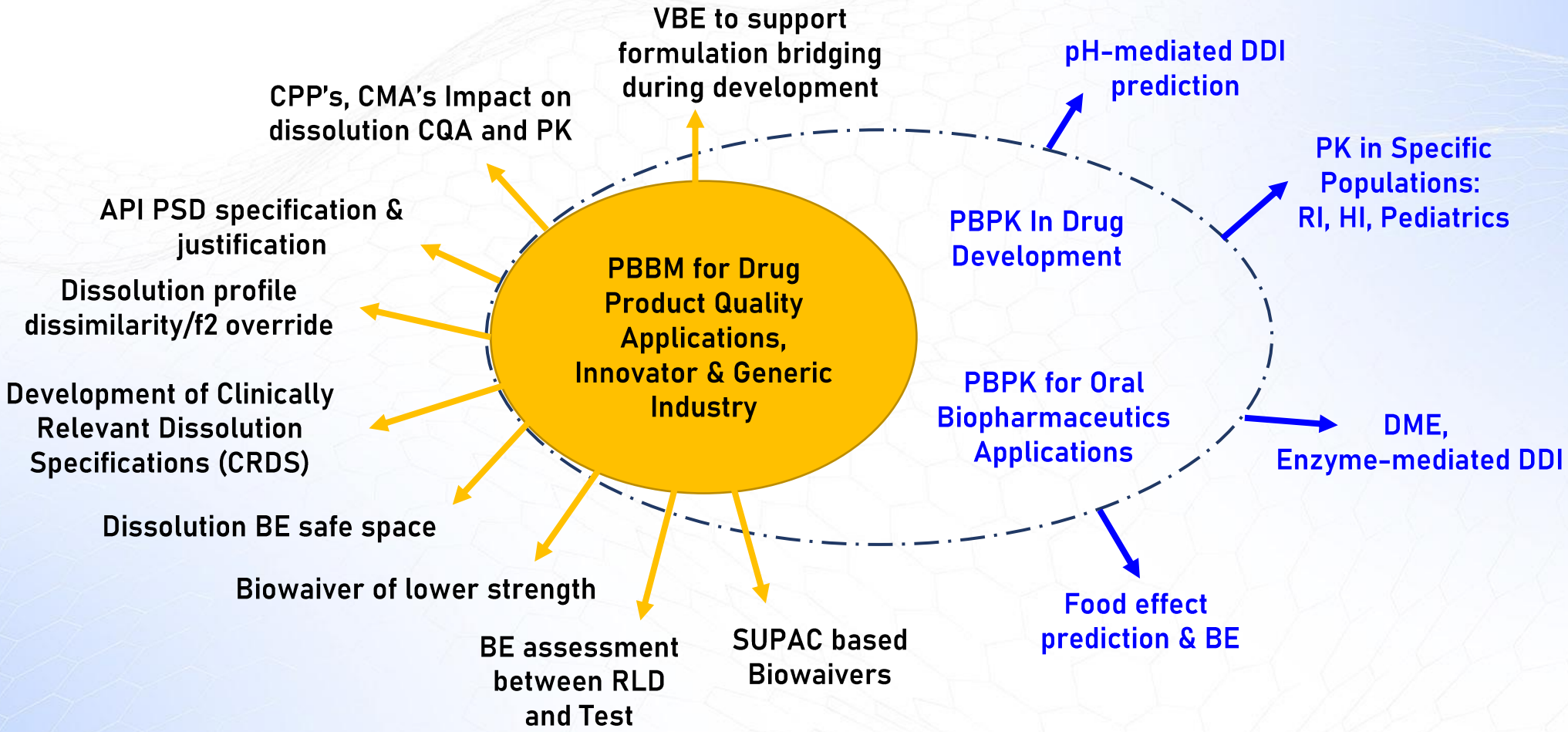
Pre-2008 applications: Parrott et al., 2005; Jones et al., 2006 (human PK and food effects).
Sources: Zhang X. and Zhao P. From a Mathematical Model to a Technology: The 100 Years' Evolution of PBPK. In The Art and Science of Physiologically-Based Pharmacokinetics Modelling and Drug–Drug Interaction, 2024.

Content prepared by human, slide polished by AI

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Physiologically Based Biopharmaceutics Models (PBBM) Within the Broader PBPK Landscape



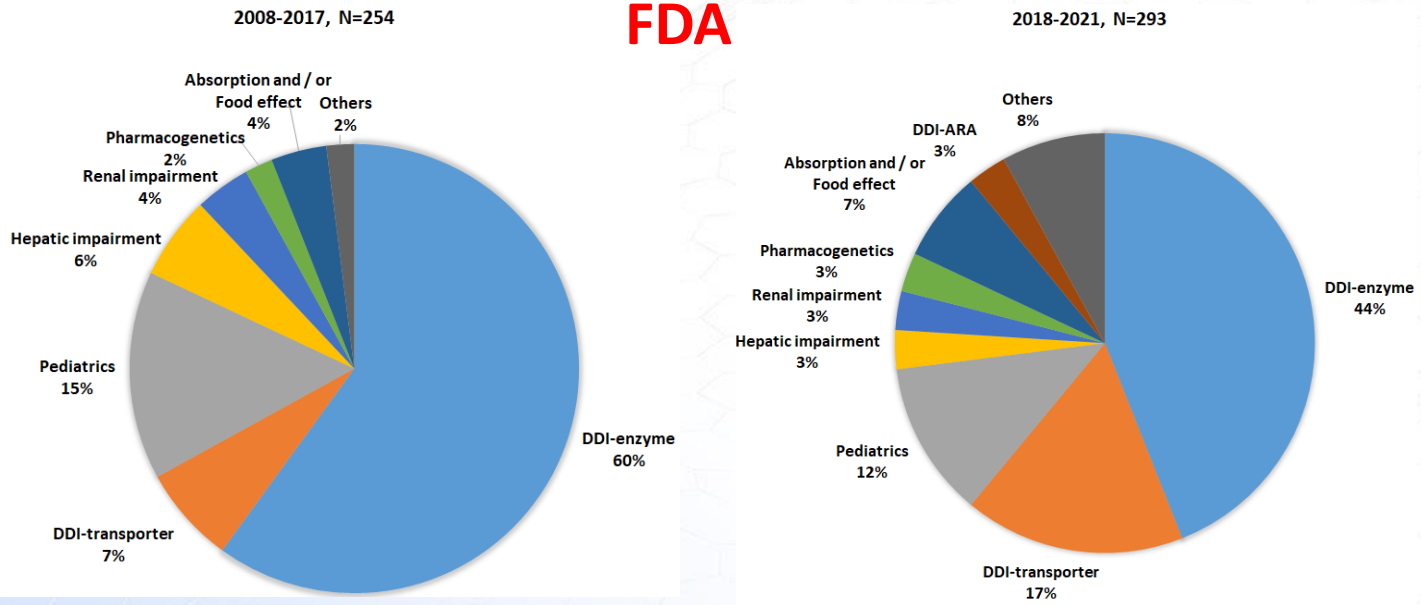
API: Active pharmaceutical ingredient, BE: Bioequivalence, CMA: Critical material attribute, CPP: Critical process parameter, CRDS: Clinically relevant dissolution specifications, DDI: Drug-Drug interactions, DME: Distribution, metabolism and excretion, HI: Hepatic impairment, PBPK: Physiologically-Based Pharmacokinetics, PSD: particle size distribution, RI: Renal impairment, RLD: reference listed drug, SUPAC: Scale-up and post-approval changes, VBE: Virtual bioequivalence

Slide courtesy of X. Pepin: Considerations for qualification of Physiologically-Based Biopharmaceutics Models - Beyond the EMA framework (2025)

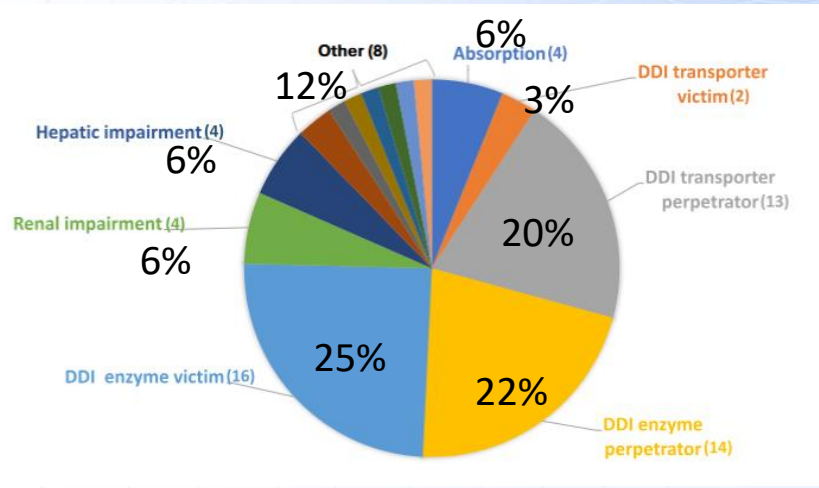
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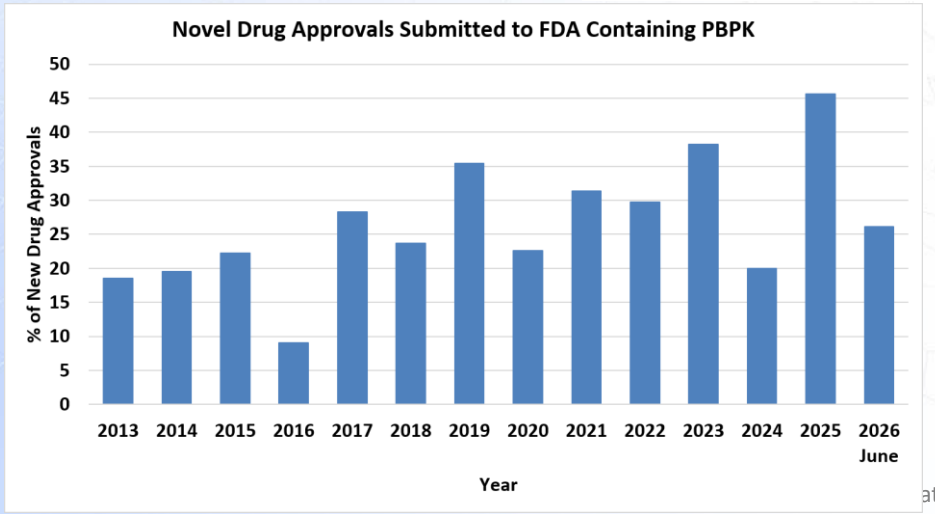
Recent Trend in Regulatory Submissions of PBPK Analyses

FDA



EMA





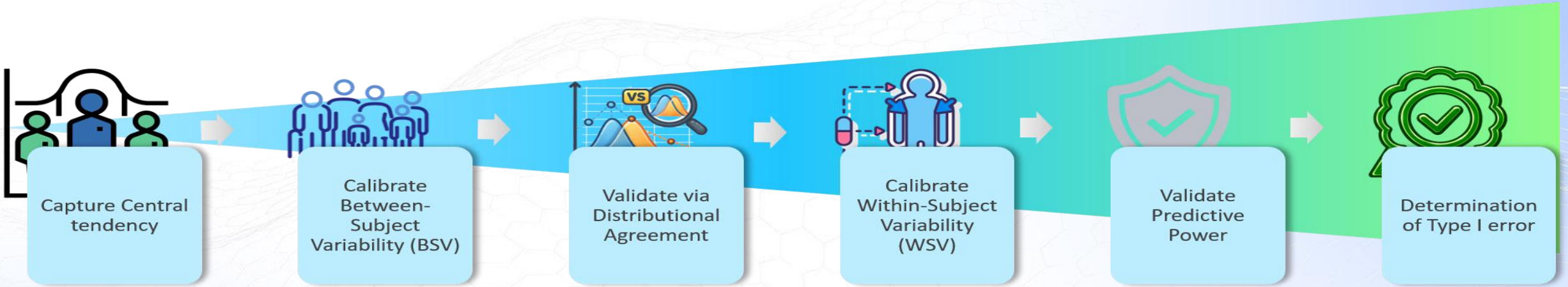
% of PBPK in marketing authorization applications (MAAs) 2022-2023 - **26% (25/95)**

- Grimstein et al. (2019) PMID: 30385284; DOI: 10.1016/j.xphs.2018.10.033
- Zhang X. et al. (2020) PMID: 33205429; DOI: 10.1002/jcph.1767
- Chu X et al. (2022) PMID: 35561140; DOI: 10.1002/cpt.2643
- Paul P. et al. (2025) PMID: 39748538; DOI: 10.1002/cpt.3525

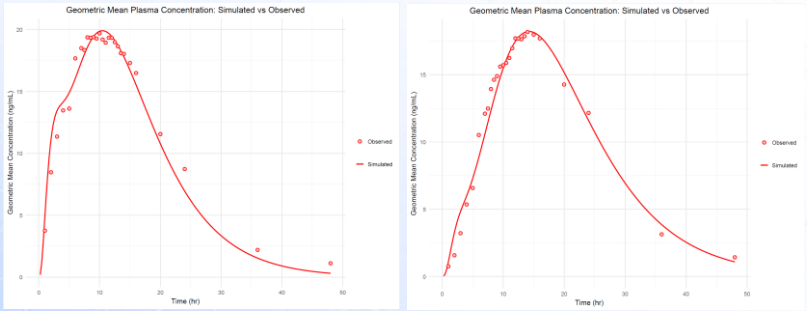
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An End-to-End Validated Framework for Virtual Bioequivalence (FDA Grant 1U01FD0079069)

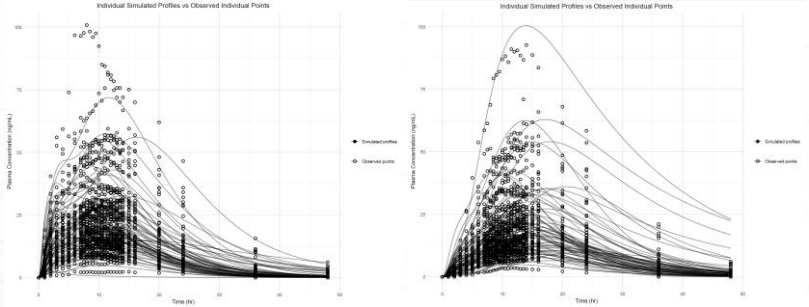
Goal: Establish a statistically sound, decision-ready workflow for PBPK-PBBM Virtual Bioequivalence



1. Mean exposure

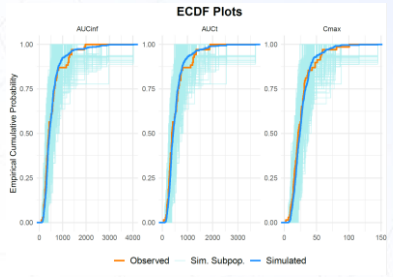


2. Between-subject variability

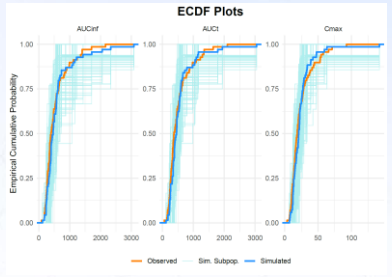


3. Distributional agreement

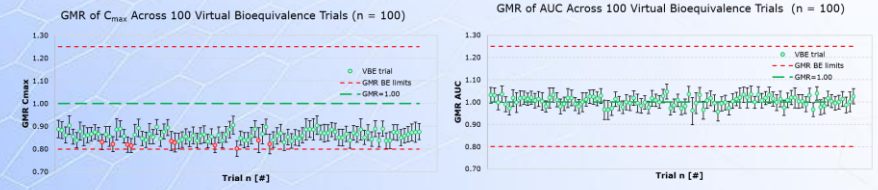
Reference



Test

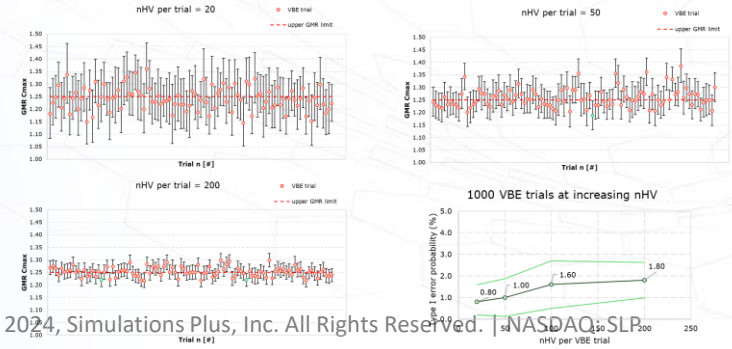


4–5. Within-subject variability and predictive power





6. Type I error



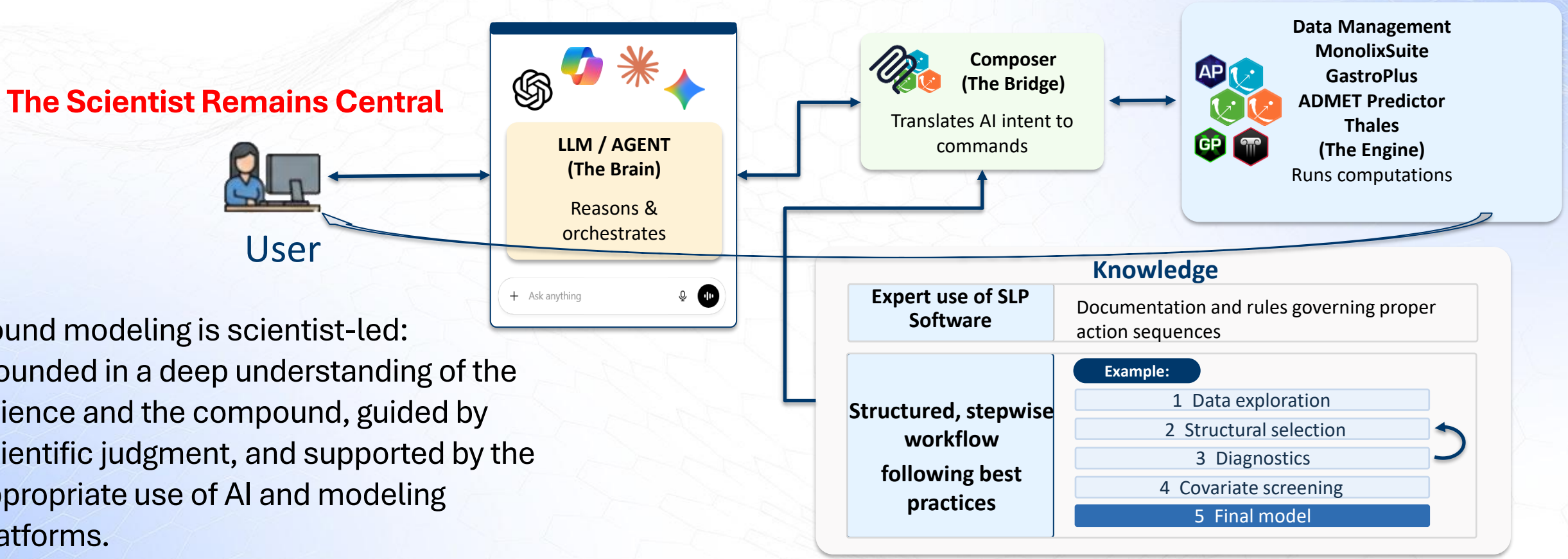
Slide courtesy of M. Pettarin

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Composer is the operating layer between conversation and science

Our dedicated MIDD operating system connecting agentic AI products to our scientific engines. Everything is anchored by our validated, well known & respected scientific engines.

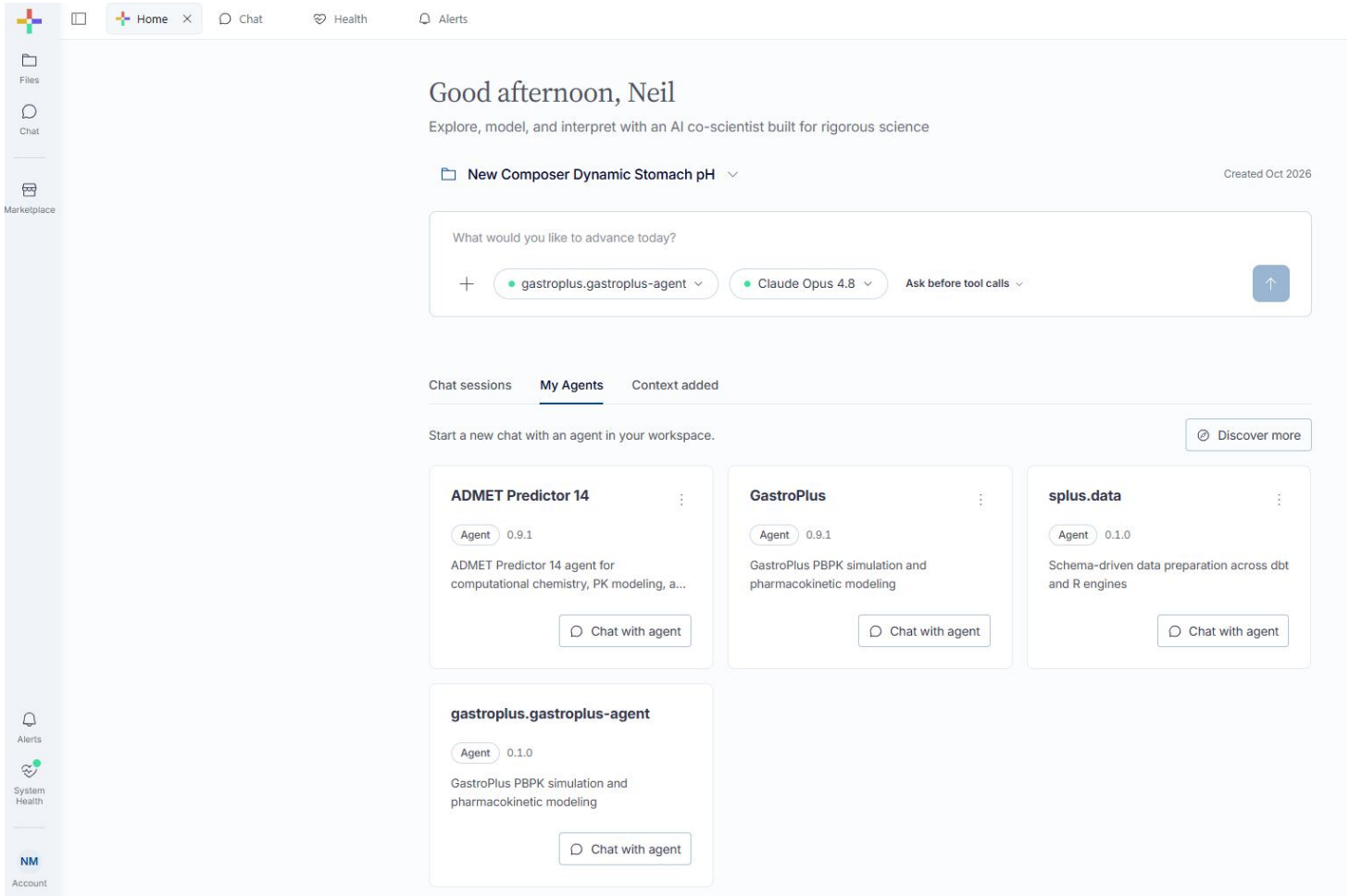


Sound modeling is scientist-led: grounded in a deep understanding of the science and the compound, guided by scientific judgment, and supported by the appropriate use of AI and modeling platforms.

Slide courtesy of P. Kilford
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THE PRODUCT

S+ Composer: one coordinated hub of scientific workflow



ONE PROGRAM, END TO END

SCIENTIST DIRECTS — **Develop an ACAT/PBPK model for oral midazolam based on the data provided in input.xlsx.**

▼

AI PARSES — **Understands directions, reasons and calls the skills and the tools to automate result with AI reasoning loop**

▼

COMPOSER — **Calls data agent (profile + transform + test), GastroPlus agent**

▼

ENGINES — **ADMET Predictor**
GastroPlus

▼

SCIENTIST REVIEWS

THE CONTEXT TRAVELS WITH THE WORK

Slide courtesy of P. Kalra, N. Miller
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