An industry perspective on high impact QSP and QST model applications in clinical drug development

Session 3: Mechanistic models for the future; challenges and opportunities in the context of MIDD & risk assessment

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An industry perspective on high impact QSP and QST model applications in clinical drug development

Anna Sher, personal position informed by the QSP/T Community of Practice at GSK

Session 3: Mechanistic models for the future; challenges and opportunities in the context of MIDD & risk assessment

HMA/EMA multi-stakeholder workshop on reporting and qualification of mechanistic models for regulatory assessment
October 8-9, 2025

The presentation draws upon the collective experience and insights of multiple pharmaceutical industry experts at GSK with experience of QSP and QST applications, with discussions facilitated by the GSK QSP/T Community of Practice.

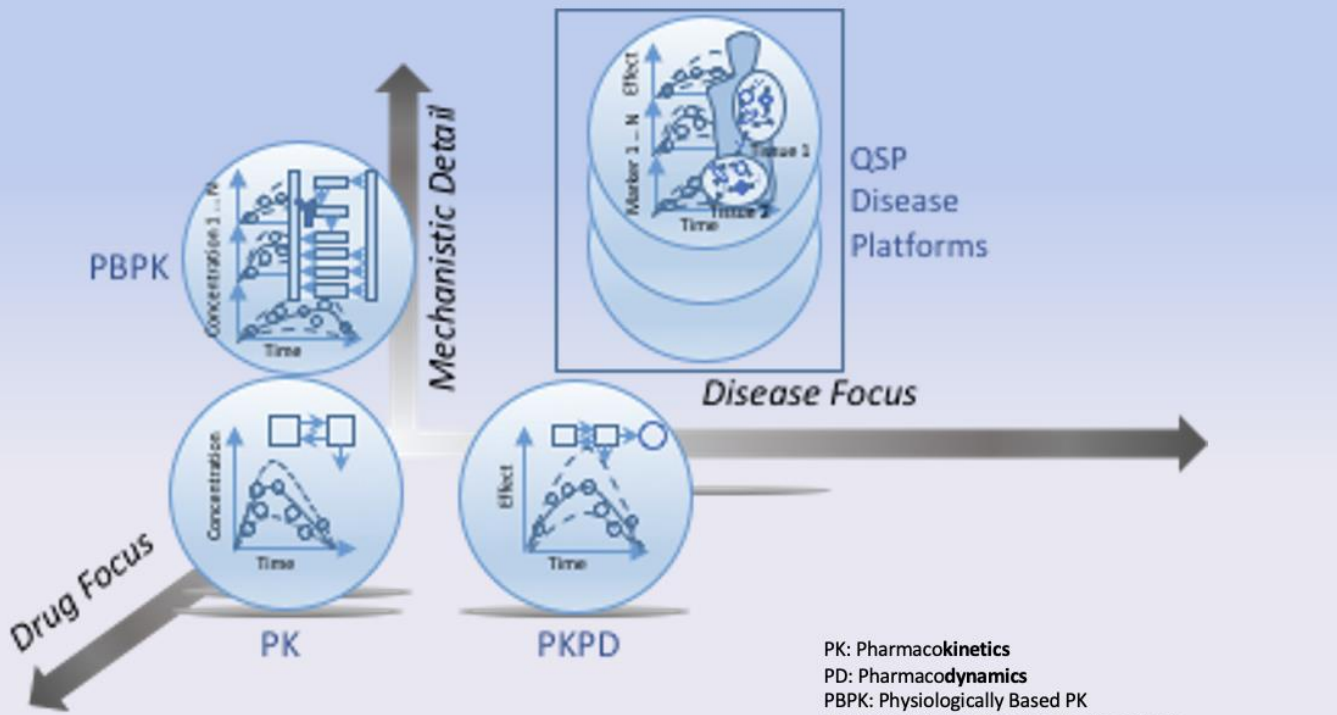
The views expressed during this presentation, as well as any commentary shared during the conference, are solely my own and do not necessarily reflect the official position or opinions of my employer, GSK.

I would like to extend gratitude to the organizers for their efforts in coordinating the presentations, facilitating the scope and providing this opportunity to participate in the HMA/EMA multi-stakeholder workshop on reporting and qualification of mechanistic models for regulatory assessment, held on October 8-9, 2025.

What is QSP?

We use mathematical modelling and simulation to describe mechanistic, time-course relationships between target modulation and disease biomarkers & clinical outcomes…

…to predict and interpret clinical response and to improve decision-making throughout the pipeline



- QSP is mechanistic modelling linking target modulation to disease modification
- QSP focus is on disease, pathways, and mechanisms
- QSP and QST are tools to generate Virtual Patients and run *In Silico* Trials
- QSP and QST provide uncertainty quantification and, hence, quantitative support for internal decision-making and regulatory interactions
- Different computational models are used in QSP/T including
  - Temporal (ordinary differential equations)
  - Spatio-temporal (partial differential equations)
  - Agent-based
  - Statistical (including Bayesian)
  - Boolean
  - Empirical curve fitting
  - Machine learning

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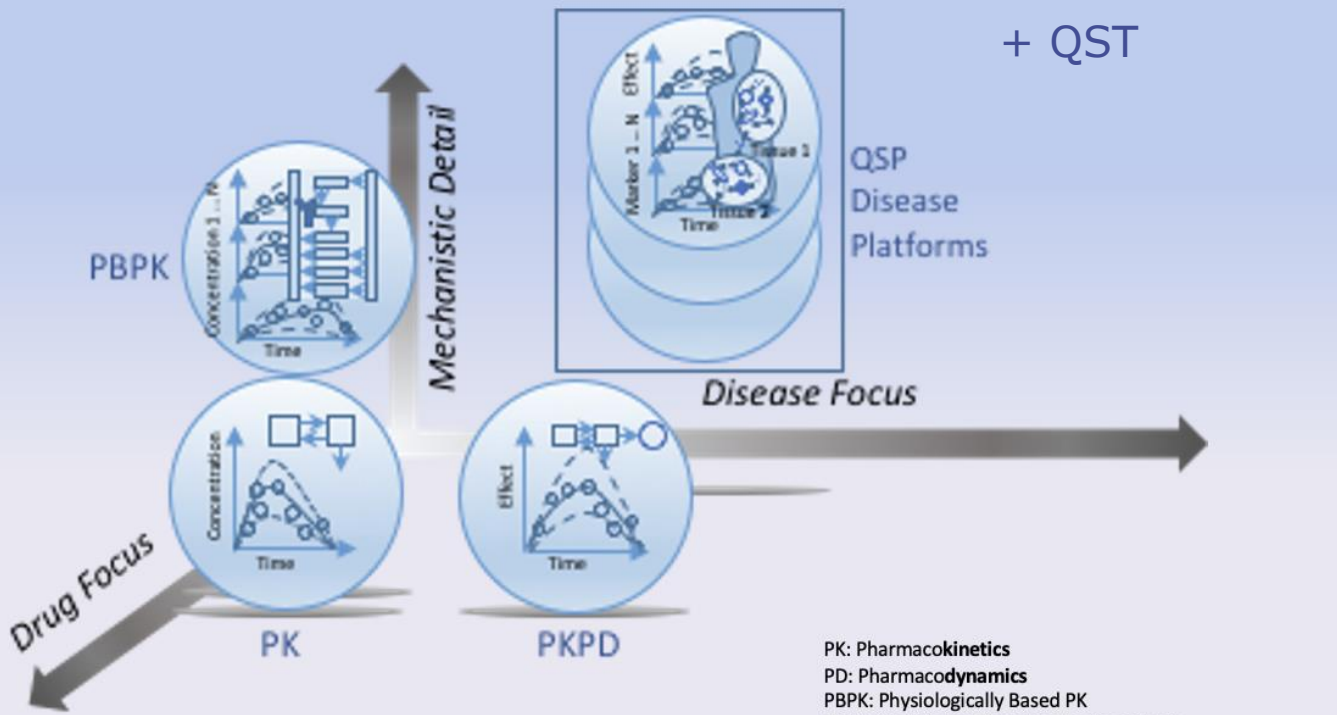

Musante et al. 2016
https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.528

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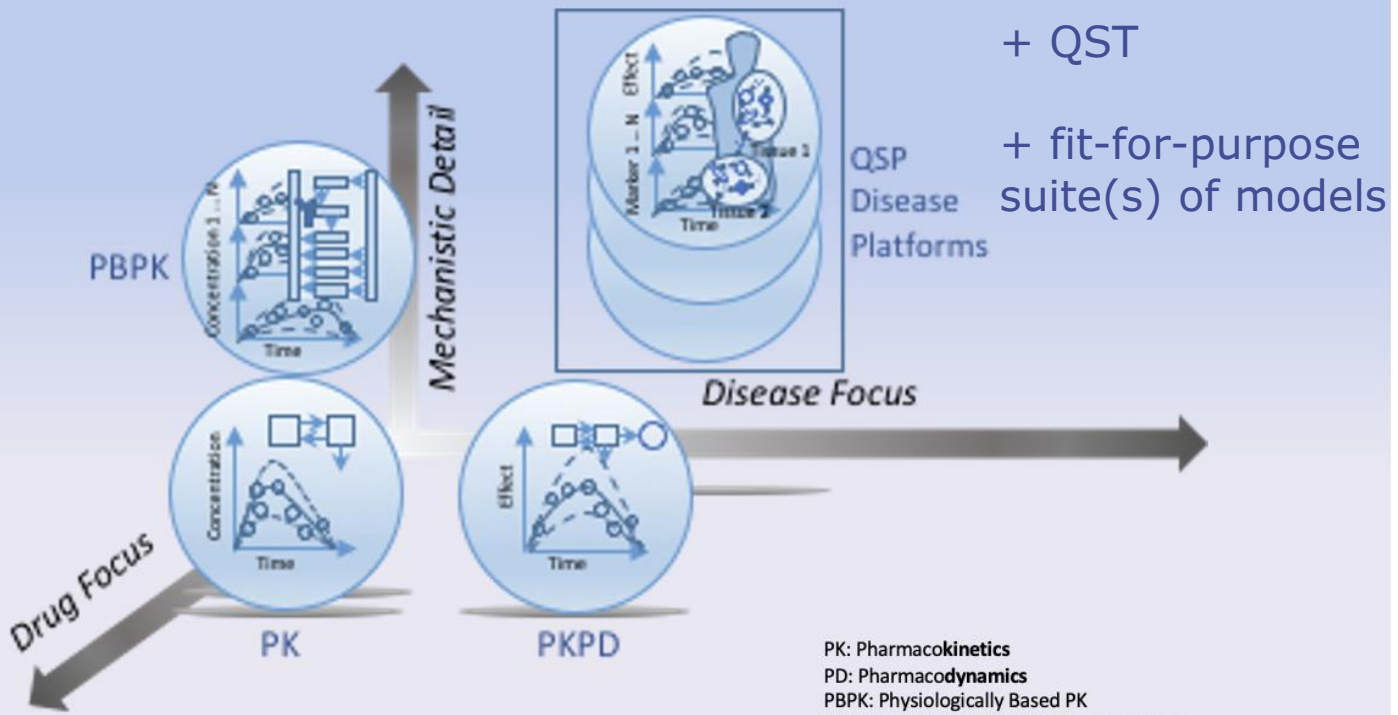

PK: Pharmaco**kinetics**
PD: Pharmaco**dynamics**
PBPK: Physiologically Based PK
QSP: Quantitative Systems Pharmacology

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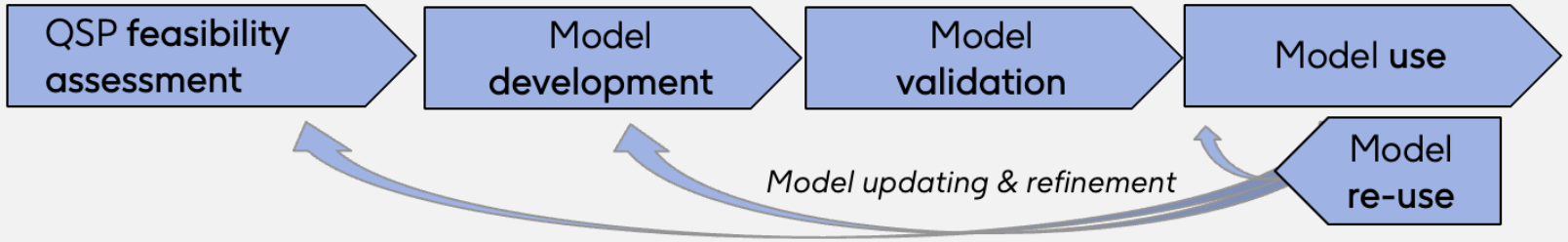
Development, applications and impact of QSP models

QSP model development process supports decision making end-to end and, especially, throughout the clinical development lifecycle...



where applications of QSP include ...

non-exhaustive list

- *Dosing Regimen Predictions*
- *Confidence in rationale of MOA*
- *Clinical study design, e.g. eligibility criteria*
- *Combination efficacy evaluation*
- *Biomarker & patient population selection & interpretation*

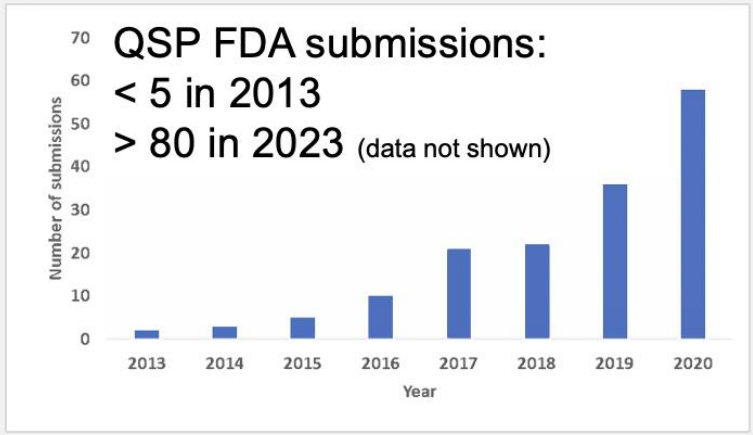
with QSP impact including ...

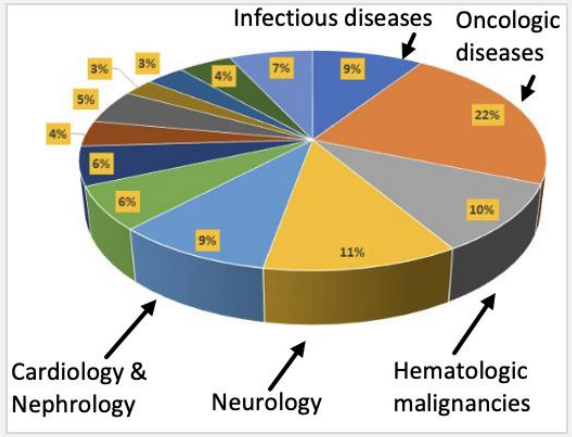
non-exhaustive list

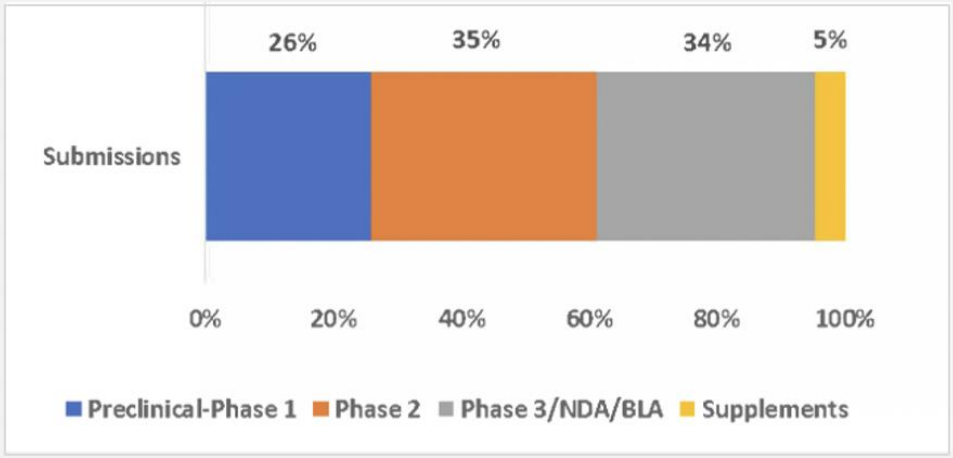
- *internal decision making at the asset level*
- *above-asset decision making (eg. portfolio prioritization, TMP, BD)*
- *support of regulatory interactions*

QSP and QST are increasingly used to support regulatory interactions

Open-source reference models are being encouraged (of note: collaborations between academia and industry increasingly provide more opportunities for publishing and peer-review of models)



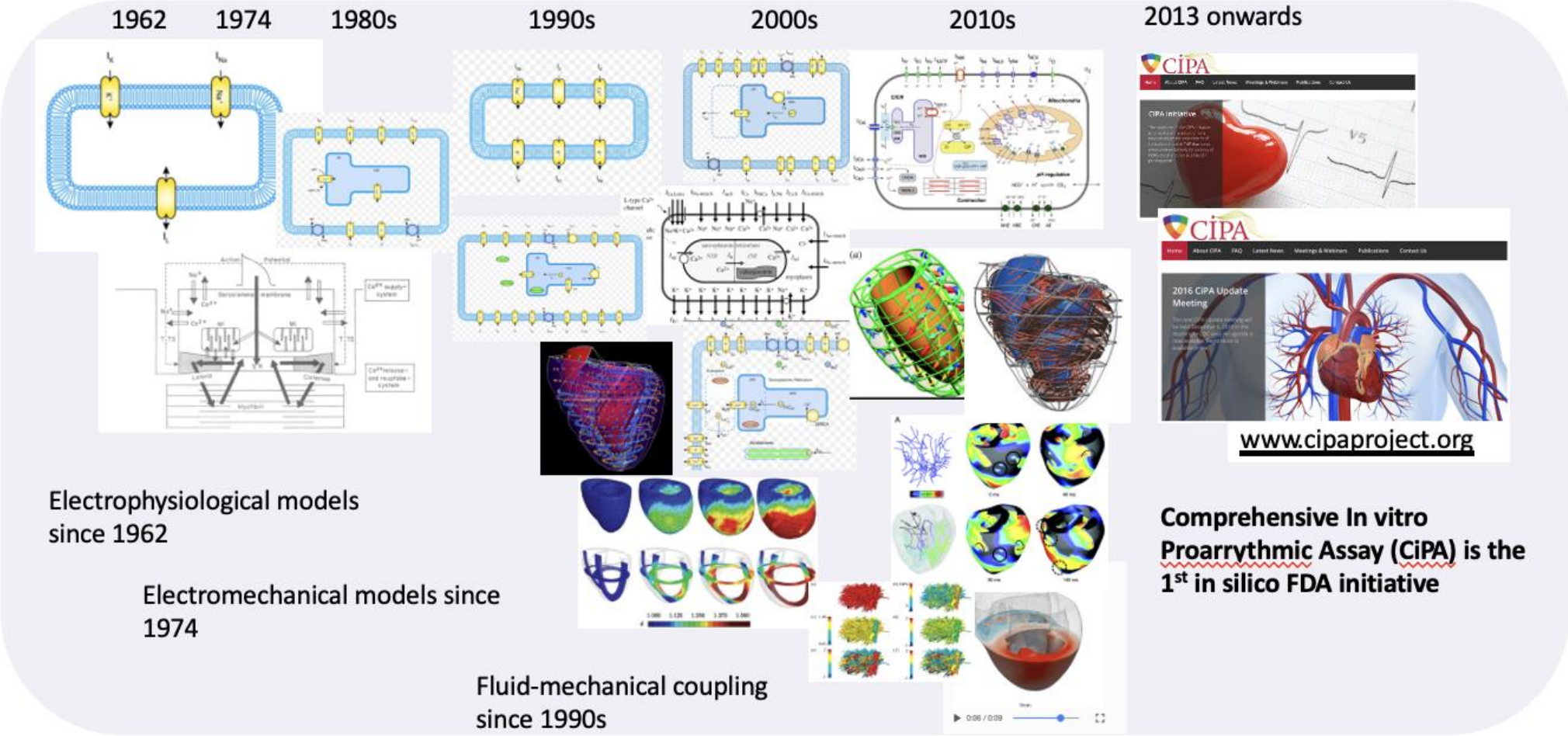




Bai et al. 2021 https://ascpt.onlinelibrary.wiley.com/doi/epdf/10.1002/psp4.12709
Bai et al. 2024 https://pmc.ncbi.nlm.nih.gov/articles/PMC11646928/

Cardiac QSP and QST modeling

Cardiac QSP and QST are among the most abundant open-source modeling, with an available curated repository of models https://models.physiomeproject.org/welcome



Neurodegenerative QSP and QST modeling

Neurodegenerative diseases is a therapeutic area example that highlights a key challenge of limited publicly available mechanistic mathematical models

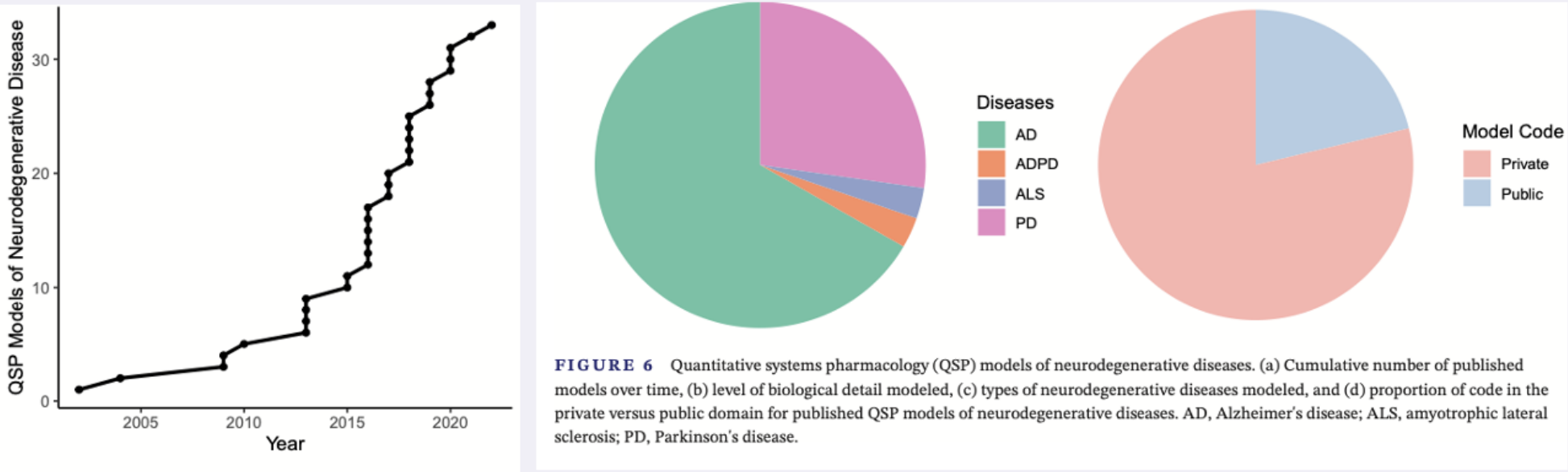


FIGURE 6 Quantitative systems pharmacology (QSP) models of neurodegenerative diseases. (a) Cumulative number of published models over time, (b) level of biological detail modeled, (c) types of neurodegenerative diseases modeled, and (d) proportion of code in the private versus public domain for published QSP models of neurodegenerative diseases. AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; PD, Parkinson's disease.

Peter Bloomingdale et al. 2021 https://ascpt.onlinelibrary.wiley.com/doi/full/10.1002/psp4.12607

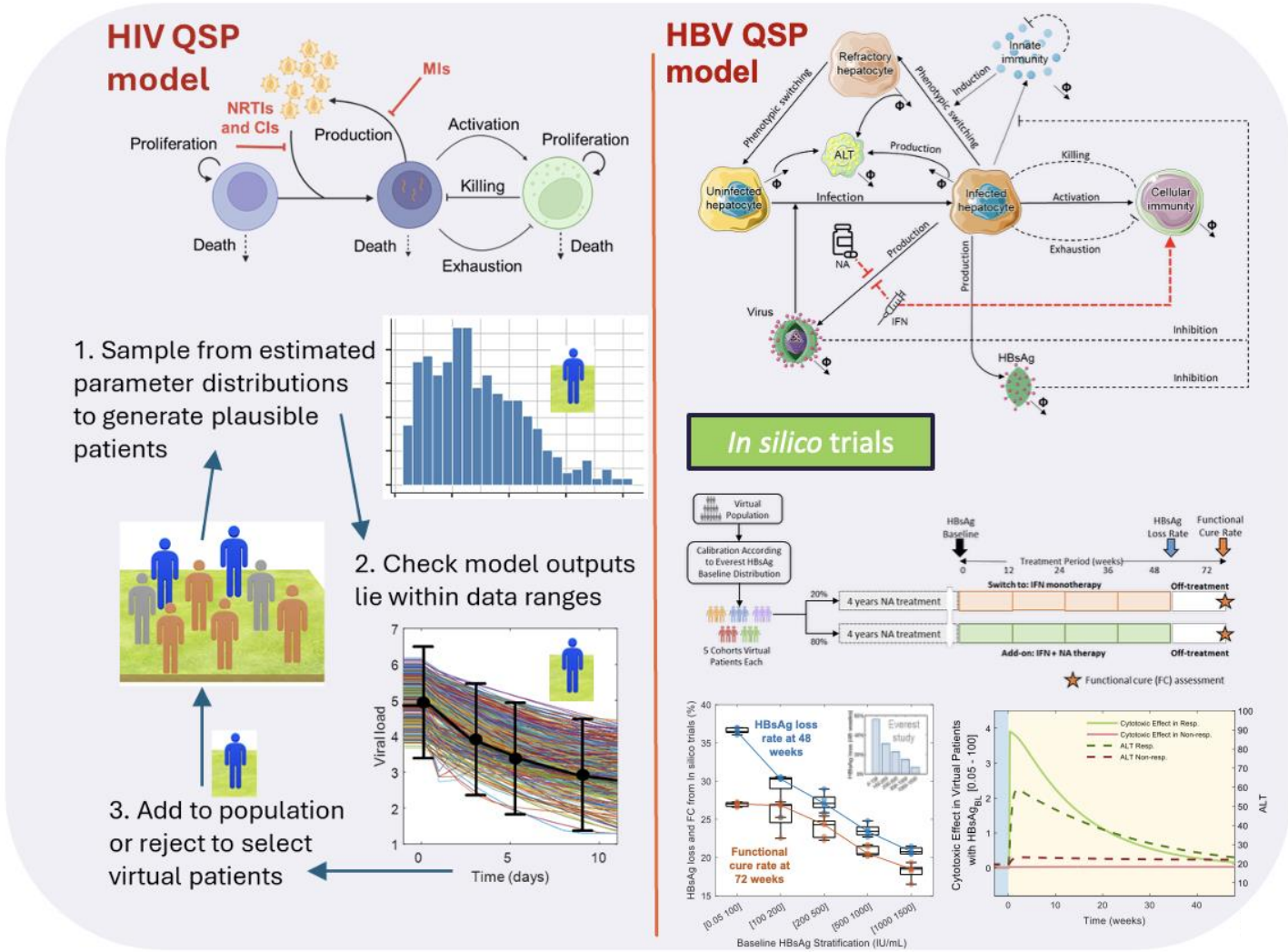
Infectious diseases QSP and QST modeling

Viral dynamics modelling such as HIV and HBV highlight the potential for developing reference, open-source QSP and QST models, calibrated and validated using publicly available clinical data

- Key viral dynamics modelling objectives
  - to develop viral dynamics models
  - to build a **predictive tool for *in silico* clinical trials** that can be applied to **different drug classes**
  - to facilitate identification of optimal **drug combinations and drug regimens** while accounting for interindividual variability
  - to **customize** these models further **to impact internal pharma portfolios**

- At GSK, we are leveraging digital twins to predict combination therapies in HIV and HBV, and inform optimal clinical trial designs

- Publications
  - Manuscript on HBV Cortes-Rios et al. 2025 https://pubmed.ncbi.nlm.nih.gov/40443045/
  - Manuscript on HIV model (in preparation)



Figures from Certara QSP Summit May 2024 (talk by Victoria Helfer); ACoP October 2024 (talk and poster by Javiera Cortes-Rios)

HBV: Hepatitis B Virus
HIV: Human Immunodeficiency Virus

Vaccine QSP/T modeling

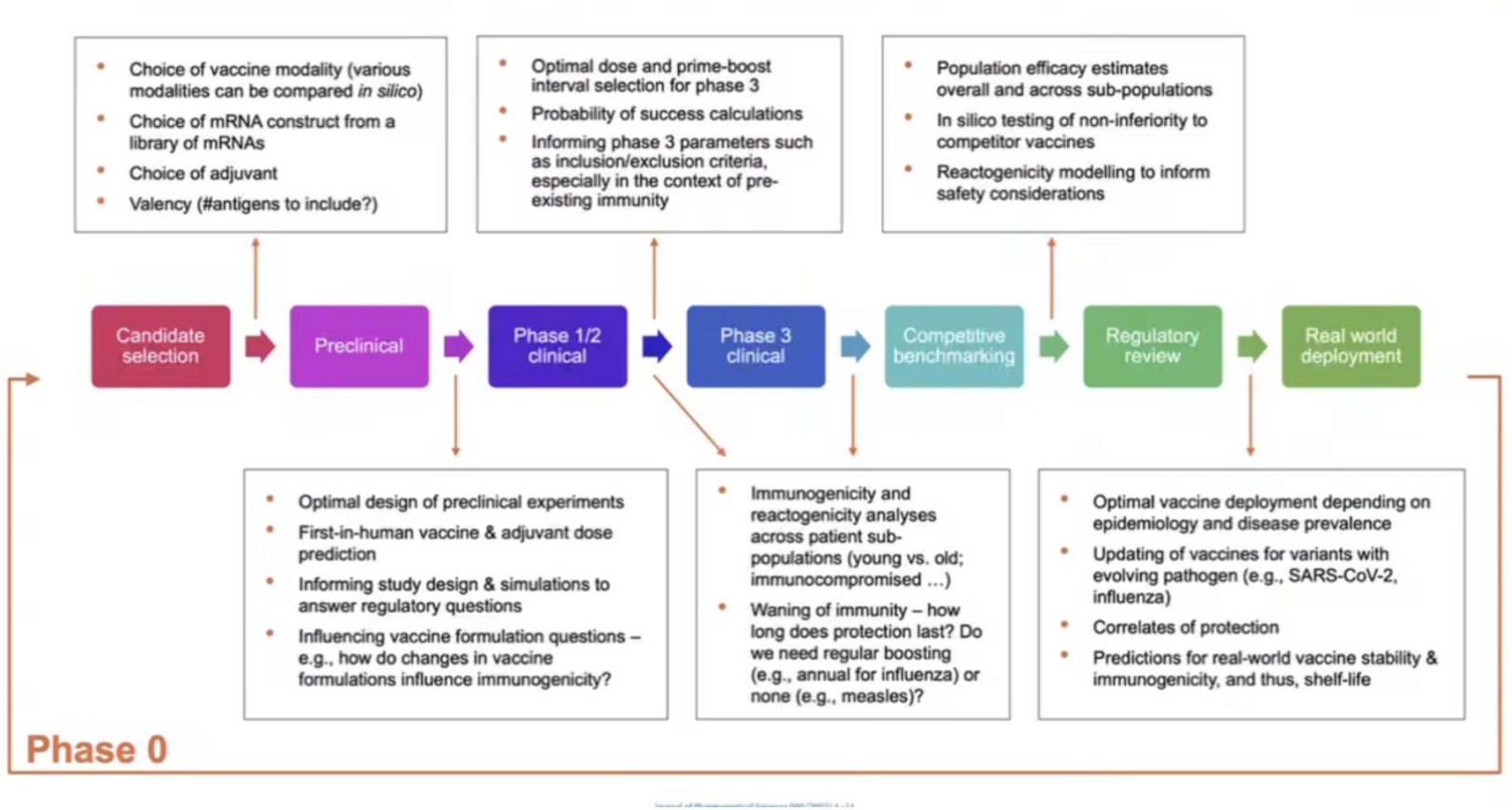
Model-Informed Vaccine Development (MIVD) is an emerging paradigm

Review > J Pharm Sci. 2024 Jan;113(1):22-32. doi: 10.1016/j.xphs.2023.10.04
Epub 2023 Nov 2.

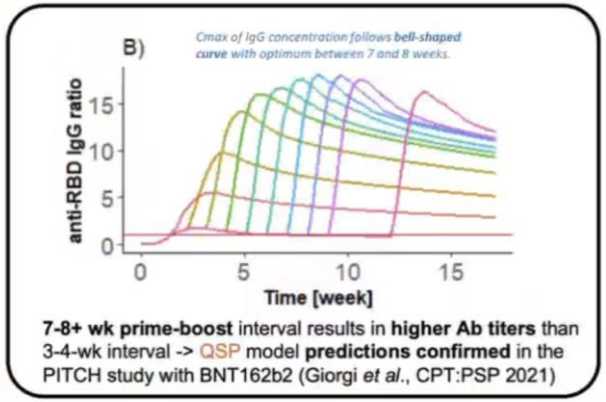
A Quantitative Clinical Pharmacology–Based Framework For Model–Informed Vaccine Development

Rajat Desikan [1], Massimiliano Germani [2], Piet H van der Graaf [3], Mindy Magee [4]
Affiliations + expand
PMID: 37924975 DOI: 10.1016/j.xphs.2023.10.043

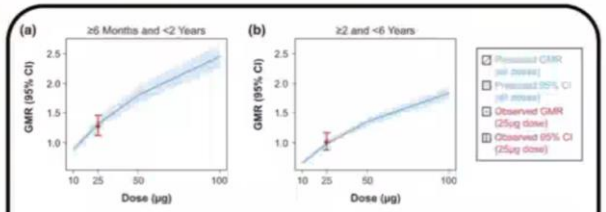
Key inflection points to be informed by QSP:



Two case studies (optimal prime-boost interval, pediatric dose selection):



7-8+ wk prime-boost interval results in **higher Ab titers** than 3-4-wk interval -> QSP model **predictions confirmed** in the PITCH study with BNT162b2 (Giorgi *et al.*, CPT:PSP 2021)



Model **calibrated to teen/adult data** successfully predicted the immunogenic response of young children (aged **2–5 years**) and infants (aged **6–23 months**) to different dose levels of the COVID-19 vaccine, mRNA-1273 -> IS/ID model **predictions confirmed** by the phase II/III pediatric KidCOVE clinical study, and informed Moderna's pediatric vaccine dose (Ivaturi *et al.*, CPT PSP 2025)

A clinical QSP/T perspective

Future is Bright	Caution is Warranted
• Huge opportunities for impacting internal decision-making in R&D, including business development • Huge growth in QSP modelling groups within pharma • QSP/T is becoming mainstream….	• Huge expectations • Many technical questions remain as technology solutions emerge • Standard processes are still under development for both drug developers and vendors
• Computational tools are exploding • Advances in software and hardware allow us to solve equations faster and process data more efficiently	• Complex landscape: external partnering with the many silos is standard practice • Very limited open source: less community-based peer-review
• ICH M15, regulatory workshops, submissions facilitates making QSP/T a part of the MIDD toolbox	• Limited community-based good practices and standards • Qualification of a particular use case, including model and/or virtual patient validation, is often subject to individual bias and preferences

Concluding remarks

Key takeaways critical to success of clinical QSP:

- **Fit-for-purpose** and **question-specific QSP and QST** modeling
- **Adapting to constantly evolving QSP and QST models** as standard practice within drug development decision-making and regulatory review
- **Close collaboration, communication and alignment** with multi-disciplinary teams (biologists, clinicians and disease-area experts) across both drug developer(s) and regulators

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Alan Richard, Pfizer
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Thank you

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