

The landscape of QSP modelling and Virtual Populations: from current to best practice

Session 3: Mechanistic models for the future: Challenges and opportunities

HMA/EMA multi-stakeholder workshop on reporting and qualification of mechanistic models for regulator

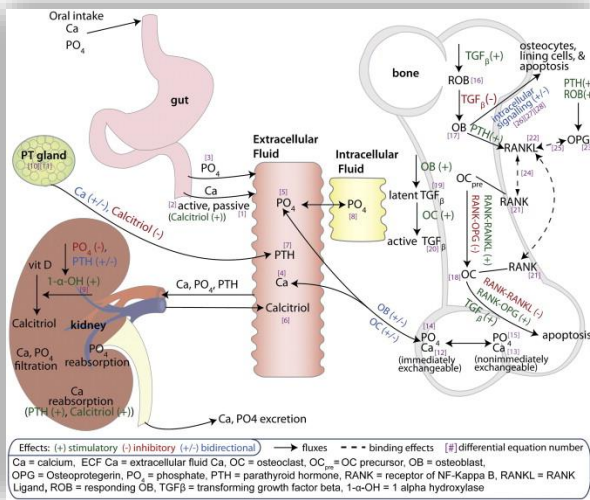
Alexander Kulesza (on behalf of the Working Group "Credibility of QSP models" within the ISOP QSP Special Interest Group (SIG))

ESQlabs GmbH, Germany
Université Namur, Belgium

Quantitative Systems Pharmacology (QSP) Modeling

Diversity in Complexity and Application

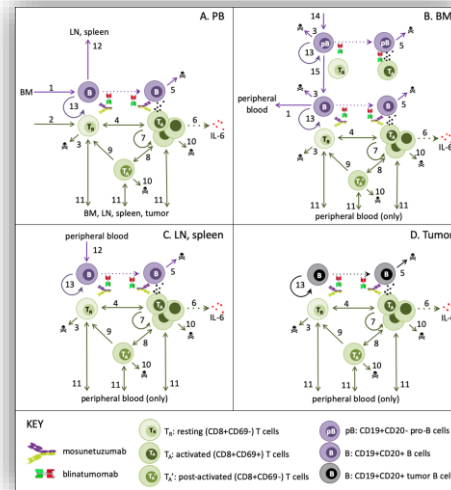
Rare endocrine disorder
Hormone analogue



10.1016/j.bone.2009.08.053

Oncology
Bispecific T-cell engager

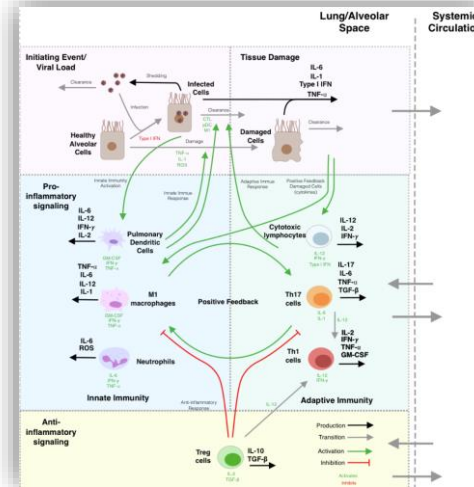
Vpop



10.3389/fphar.2022.910789

Viral infection
Antiviral therapy

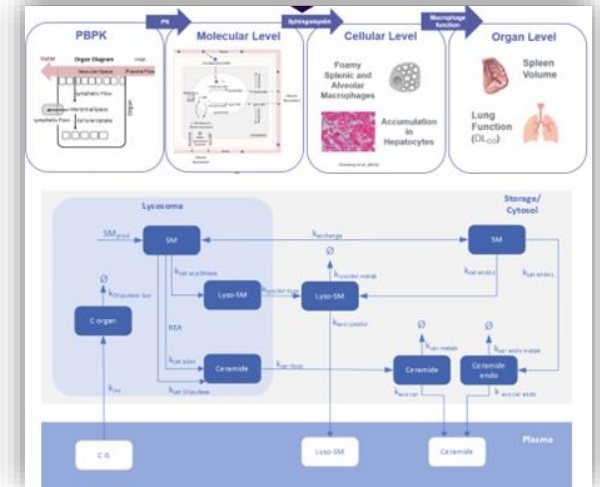
Vpop



10.1038/s41540-023-00269-6

Rare genetic enzyme deficiency
Enzyme replacement

Vpop



10.1002/psp4.12304

- QSP models are diverse by design: many biological scales, various disease areas, wide range of therapeutic modalities
- Diverse datasets used for model calibration and validation

Credibility assessment of QSP models

What we have so far: Frameworks, White Papers, Surveys

Scientific and regulatory evaluation of mechanistic *in silico* drug and disease models in drug development: Building model credibility

Flora T. Musuamba ✉, Ine Skottheim Rusten, Raphaëlle Lesage, Giulia Russo, Roberta Bursi, Luca Emili, Gaby Wangorsch, Efthymios Manolis, Kristin E. Karlsson, Alexander Kulesza ... [See all authors](#) ▾

CPT:PSP (2021)

Evaluation framework for systems models

Sietse Braakman, Pras Pathmanathan, Helen Moore ✉

CPT:PSP (2021)

Assessing the performance of QSP models: biology as the driver for validation

Fulya Akpınar Singh¹ • Nasrin Afzal¹ • Shepard J. Smithline¹ • Craig J. Thalhauser¹

JPKPD (2024)

- **Assessment strategy should depend on Context of Use**
- **Community has developed a catalogue of assessment items**
- **Biology as a driver can and should be leveraged in validation**

A Flexible Approach for Context-Dependent Assessment of Quantitative Systems Pharmacology Models

[Saroja Ramanujan](#)^{1,✉}, [Jason R Chan](#)², [Christina M Friedrich](#)³, [Craig J Thalhauser](#)⁴

CPT:PSP (2019)

Current practices for QSP model assessment: an IQ consortium survey

[Jason R Chan](#)^{1,✉}, [Richard Allen](#)², [Britton Boras](#)³, [Antonio Cabal](#)⁴, [Valeriu Damian](#)⁵, [Francis D Gibbons](#)⁶, [Abhishek Gulati](#)⁷, [Iraj Hosseini](#)⁸, [Jeffrey D Kearns](#)⁹, [Ryuta Saito](#)¹⁰, [Lourdes Cucurull-Sanchez](#)¹¹, [Jangir Selimkhanov](#)¹², [Andrew M Stein](#)¹³, [Kenichi Umehara](#)¹⁴, [Guanyu Wang](#)¹⁵, [Weirong Wang](#)¹⁶, [Susana Neves-Zaph](#)

JPKPD (2024)

BUT

Current practice is highly variable among stakeholders

Credibility assessment of QSP models

What we have so far: Use cases of regulatory use of QSP

Results

Table 1. QSP model comparison

	Olipudase Alfa ¹	Paxlovid ²	Elranatamab ³
Disease description	Acid sphingomyelinase deficiency (ASMD)	Coronavirus disease 2019 (COVID-19)	Multiple myeloma (MM)
Available treatment upon submission	No disease-specific treatments available	Remdesivir, baricitinib (EUA), tocilizumab (EUA)	Several e.g., Daratumumab + Lenalidomide/Dexamethasone (RD), Bortezomib and Teclistamab
Drug's MOA	Enzyme replacement therapy (ERT)	Protease inhibitor for coronavirus replication	Bispecific antibodies (BsAbs)

Path to Regulation

Guansheng Liu, Yucheng
Office of Clinical Pharmacology,
US Food and Drug Administration

Introduction

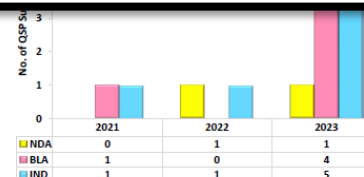
In recent years, Quantitative systems pharmacology modeling has gained significant traction in drug development. The analysis has been used in drug development and submitted to Pharmacology (OCP) to support assessment discusses challenges in developing complex and multiscale models and summarizes how a risk-informed credibility assessment framework was applied for evaluating QSP modeling in select regulatory submissions.

Objective

QSP models have been developed and used in all stages of drug development to inform, for example, the selection of dose regimen and trial design, and support safety assessments. This assessment provides an overview of QSP modeling, and analyses submitted to Center for Drug Evaluation and Research from 2021-2023 and discusses key regulatory considerations from the review of select QSP models.

Methods

By following the V&V40 standard (an FDA-recognized standard that provides a risk-based framework for establishing the credibility requirements of a computational model), three case studies are summarized and presented to demonstrate the considerations and practice when reviewing a QSP model (e.g., assessments on model structure, model assumptions, biomarker selection, parameter calibration and optimization, virtual population (VP) generation, model validation and model application) for regulatory purpose.



Conclusions

The V&V40 model credibility framework allows reviewers to effectively review submitted QSP analyses. Within the V&V40 framework, credibility assessments on the major QSP components (i.e., model structure and parameters, model validation and virtual population) depend on evaluation of model risk (model influence, decision consequence and overall model risk) for individual cases. In addition, reviewers are still accumulating experience to establish a good review practice for QSP modeling.

References

1. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761261Orig1s000IntegratedR.pdf
2. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/217188Orig1s000IntegratedR.pdf
3. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/761345Orig1s000MultidisciplineR.pdf

Disclaimer

The views expressed are those of the authors and do not reflect official policy of the FDA.

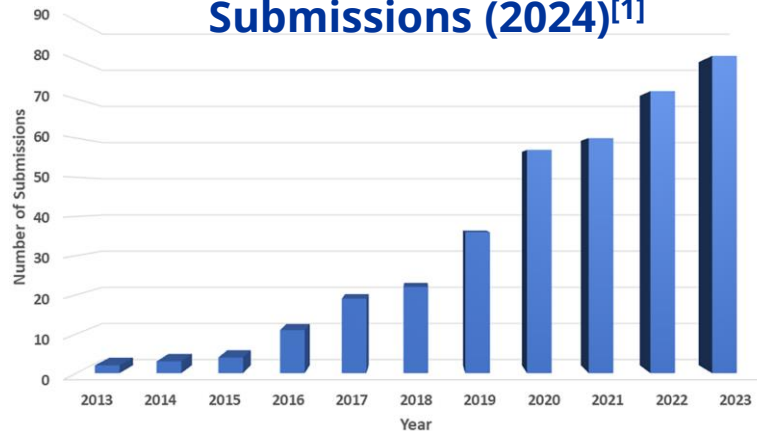
- Use cases are useful but only a snapshot of past submissions
- Not clear if case studies represent totality of best practices moving ahead, best for the practitioner community to agree on minimal set

Working Group on Credibility Assessment of QSP for Regulatory Use

Working Group launched on 11/2024 under the umbrella of ISoP QSP SIG

Motivation

Landscape Analysis for QSP in US Regulatory Submissions (2024)^[1]



[1] Bai JPF et al. Landscape of regulatory quantitative systems pharmacology submissions to the U.S. Food and Drug Administration: An update report. *CPT PSP*, 2024; 00: 1-9.

- Despite increasing number of regulatory submissions with QSP MIDD components, there is still **no regulatory guidance that addresses the specific qualification and reporting requirements of QSP models** to be acceptable for supporting regulatory decision making.
- QSP practitioners gather in a Working Group to evaluate current landscape through QSP SIG

Primary Goals

- **Identify** typical regulatory Context of Use scenarios of QSP models ,
- **Propose guidance** to assess their **credibility** and to **report** them,
- Work in **collaboration with QSP community & agencies through webinars, conference/workshop sessions, white papers on best practices.**

Working Group Deliverables (3-year charter)

WORKSHOP ON
CREDIBILITY OF
VPOPS AT
RUTGERS UNI,
MAY 2025

WHITE
PAPER:
MODEL
CREDIBILITY
Y 2026

CROSS-
INDUSTRY
CASE STUDY:
CREDIBILITY
OF TCE QSP
2027

WHITE
PAPER:
REPORTING
2025

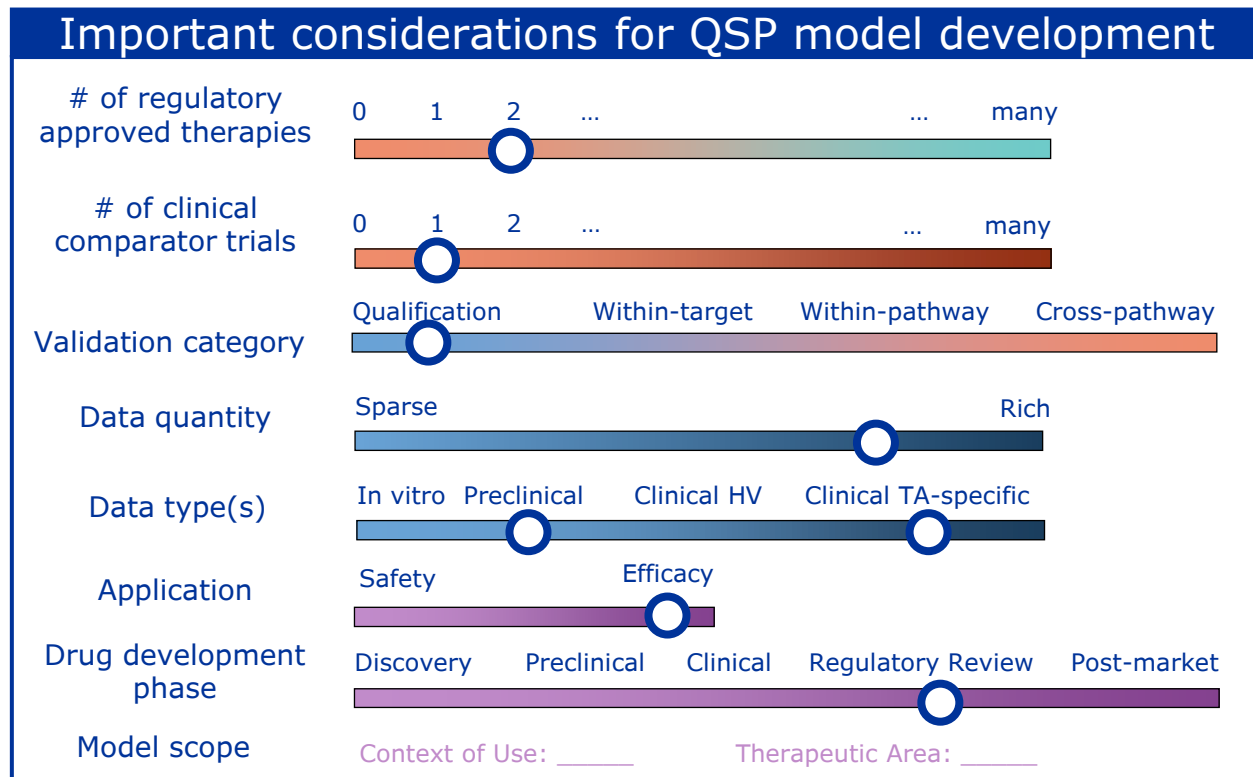
WEBI-
NARS
2026

Members: Blerta Shtylla (Chair, Pfizer), Steve Chang (Sims+), Jingqi Gong (GSK), Abhishek Gulati (Merck), Alexander Kulesza(ESQLabs), Alexander Ratushny (BMS), Conner Sandefur (Sims+), Brian Schmidt (Mardrigal), Fulya Singh (Genmab), Monica Susilo (Genentech), Weirong Wang (JnJ), Susana Zaph (Sanofi)

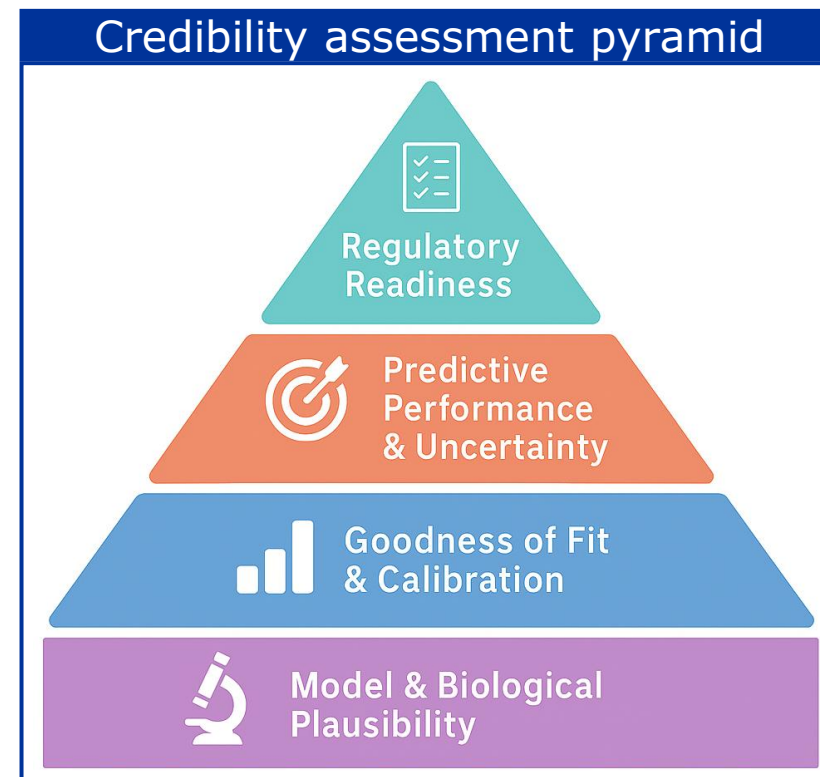


Credibility assessment of QSP models

Data, Development Phase and Context of Use



Braakman 2022 [PMID 34921743], Chan 2024 [PMID 35953664], Chang 2025 [VPOP Credibility Workshop, Rutgers University, 2025/05/19], Musuamba 2021 [PMID 34102034], Ramanujan 2019 [PMID 30983158], Singh 2024 [PMID 37386340]



Multidimensional elements underlying QSP model development, which drive inter-model diversity, can be aligned to a four-component assessment framework.

Spotlight on Virtual Populations

Align on broader terminology to encompass virtual patients and digital twins

Virtual Subject/Virtual Patient = Single structure & parameterization of the model yielding virtual measurements within ranges of corresponding data

- subject = animal, human, cell, pathway, ...

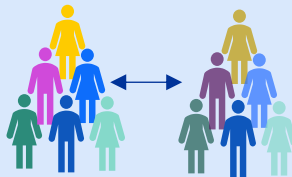
Digital Twin = Virtual subject(s) that reproduce selected features of corresponding individual subject (e.g. clinical trial patient, individual cyno)

Virtual Population (VPOP) = Set of virtual subjects that statistically reproduce selected statistical features of corresponding population data (e.g. clinical trial population)

“Traditional VPOP”:

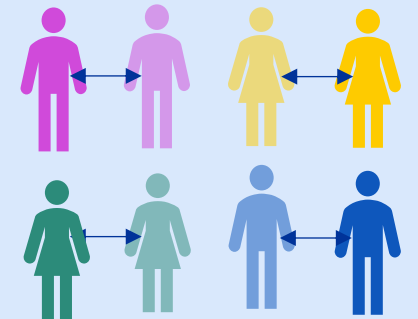
The VPOP as a whole captures the observed statistics of the true clinical population of interest.

Each virtual patient in the virtual population may not directly correspond to an actual individual patient



“digital twin VPOP”

The VPOP consists of digital twins which directly correspond to actual individual patient in the clinical cohorts



M. Susilo & J. Gong, Establishing QSP Virtual Population (VPOP) Credibility Assessment Workshop, May 19th, 2025, Rutgers University

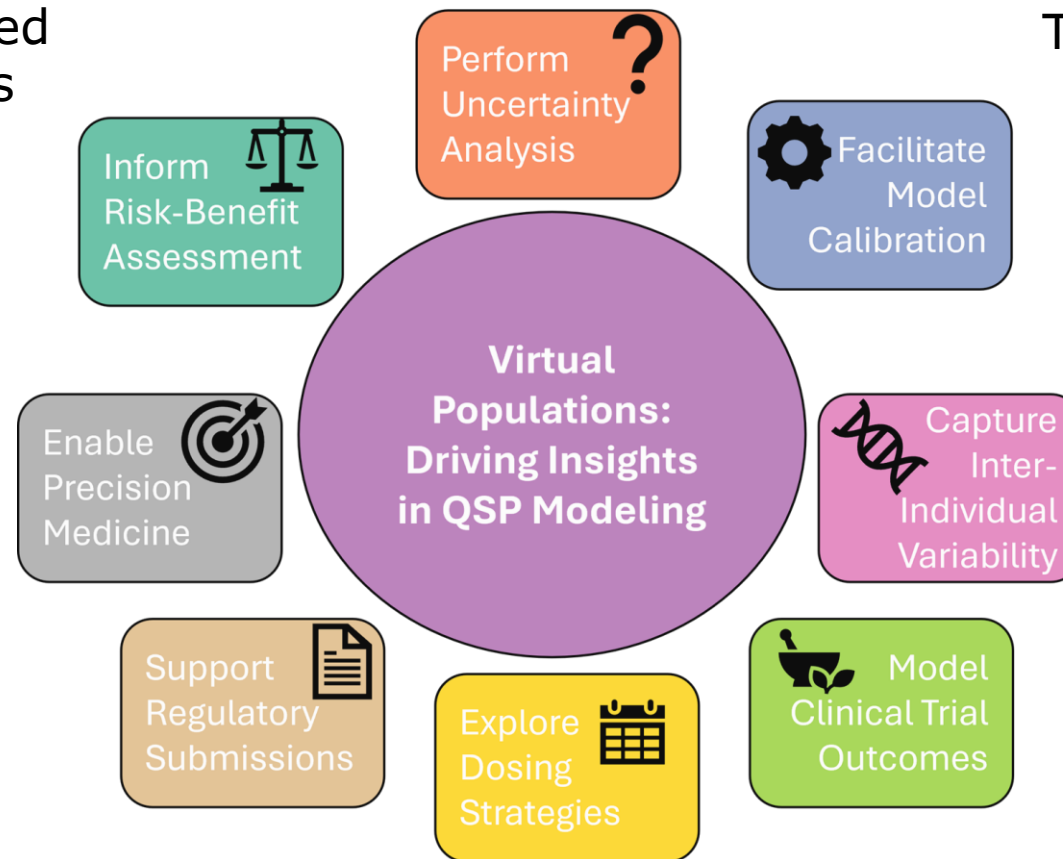
Spotlight on Virtual Populations

Diversity in application

Virtual Populations (VPops) are an important part of QSP modeling workflows and **serve many purposes that may impact model credibility assessment**

Individualized predictions

Technical tool



Between-subject, population, subgroup, arm, trial differences

S. Chang, Establishing QSP Virtual Population (VPOP) Credibility Assessment Workshop, May 19th, 2025, Rutgers University

Spotlight on Virtual Populations

Some examples of metrics for assessment

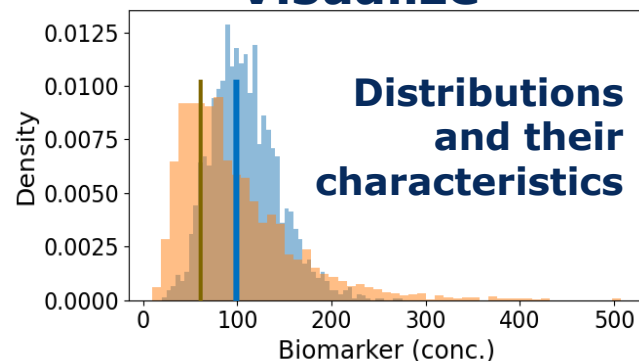


Volume 51, Issue 5

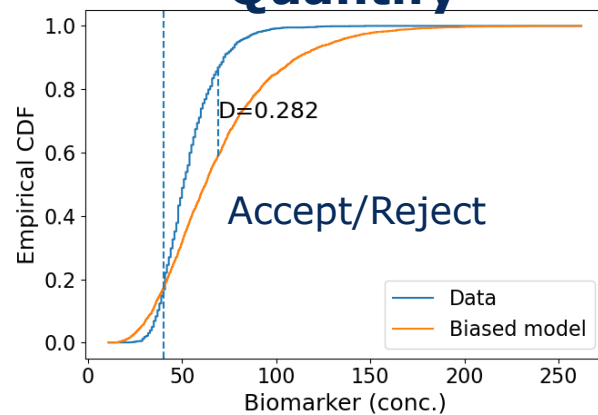
October 2024

Dual Themed Issue: PBPK of Novel Modalities & Assessing QSP Models and Amplifying their Impact

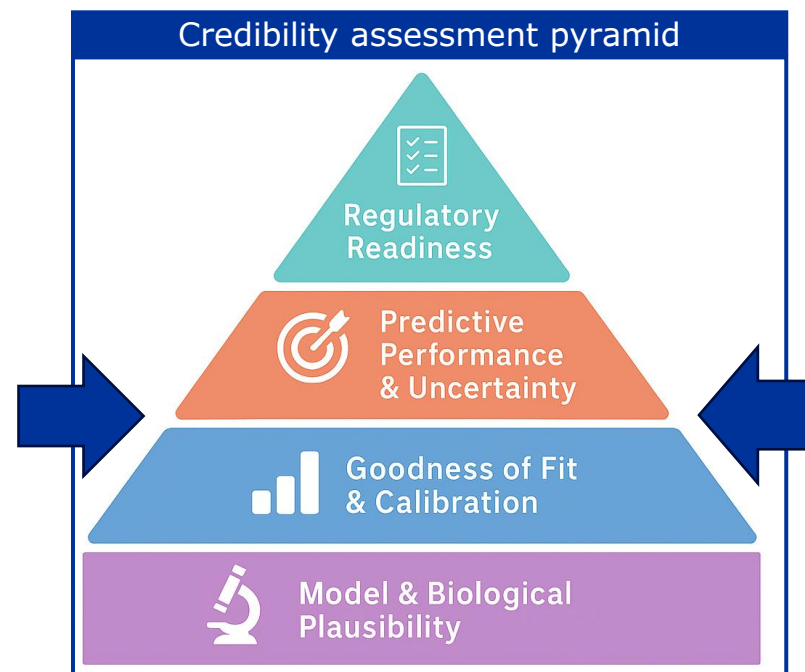
Visualize



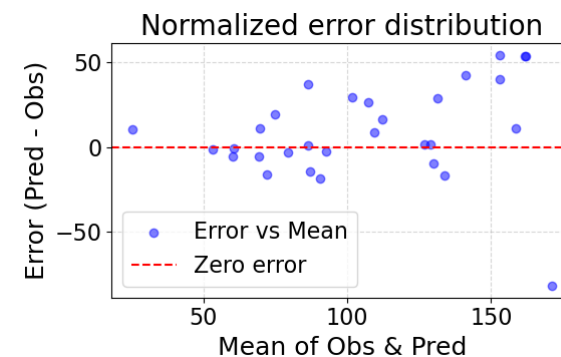
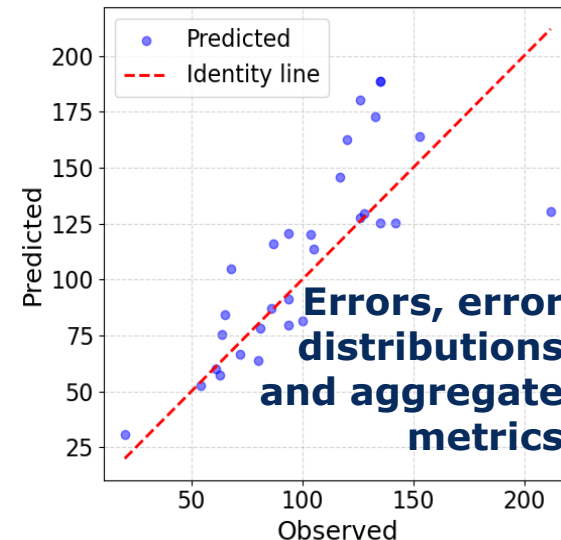
Quantify



Mock example illustrating us for traditional Vpops, example used in Allen, 2016



- Selection driven by context of use
- Typically aligned with calibration
- Should be gauged against acceptability criteria

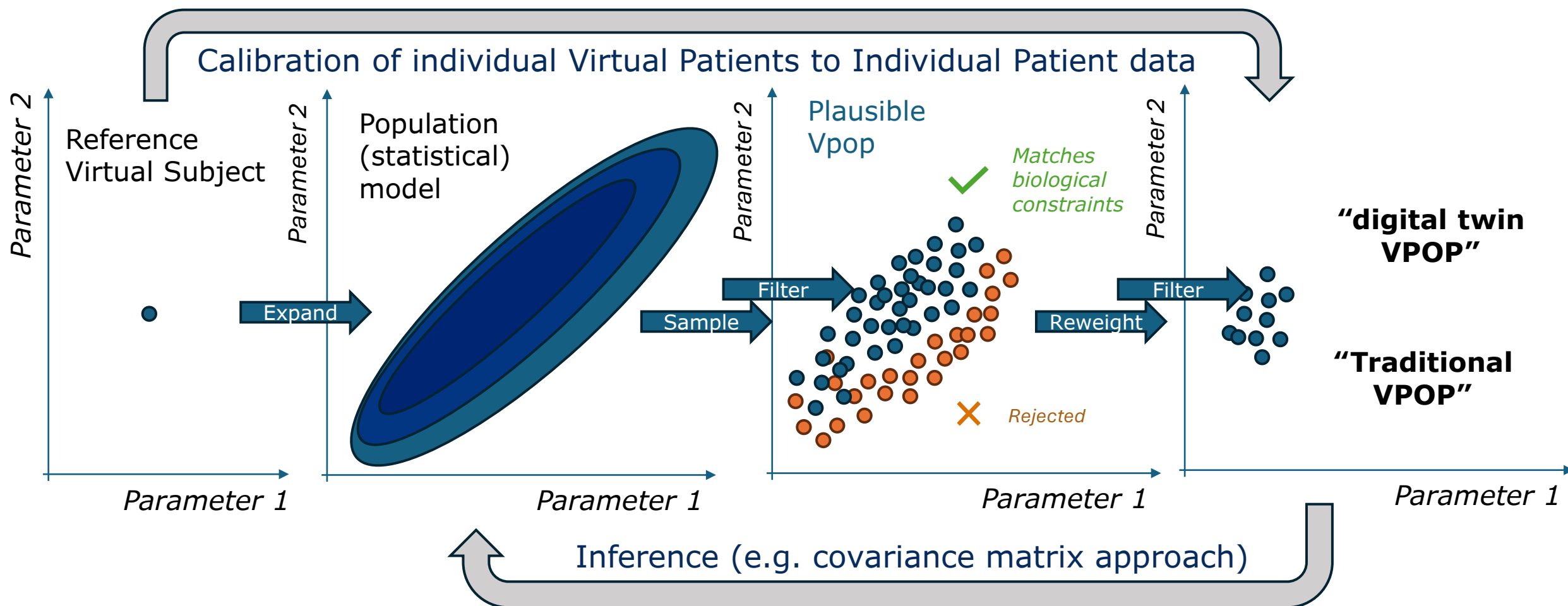


Spotlight on Virtual Populations



<https://github.com/BMSQSP/QSPToolbox>
<https://github.com/openPfizer/vpop-gen>

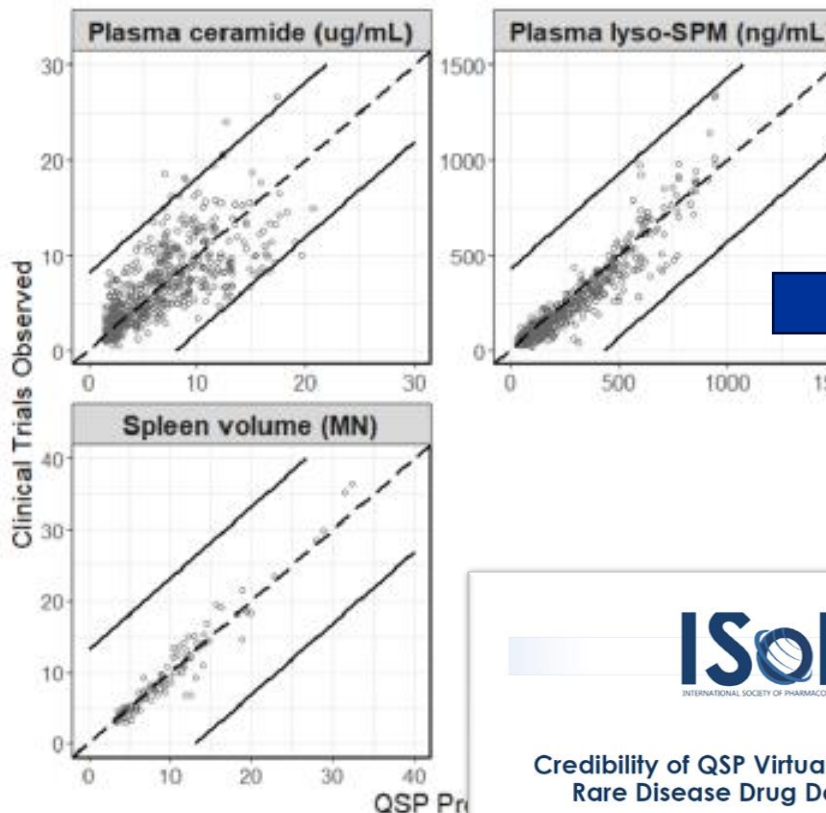
Example workflows using open source "toolbox" of Vpop methods available in publications/public github repositories



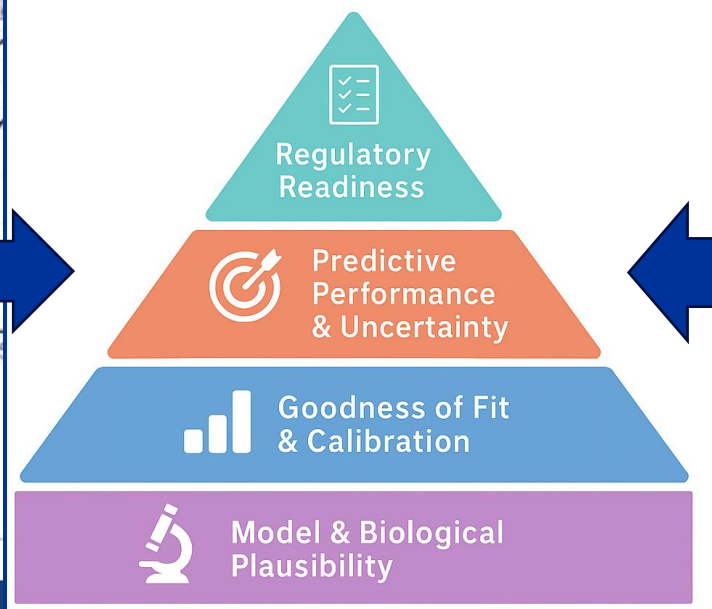
Spotlight on Virtual Populations

Evaluating uncertainty within Context of Use

Hybrid Digital Twin – Vpop



Credibility assessment pyramid

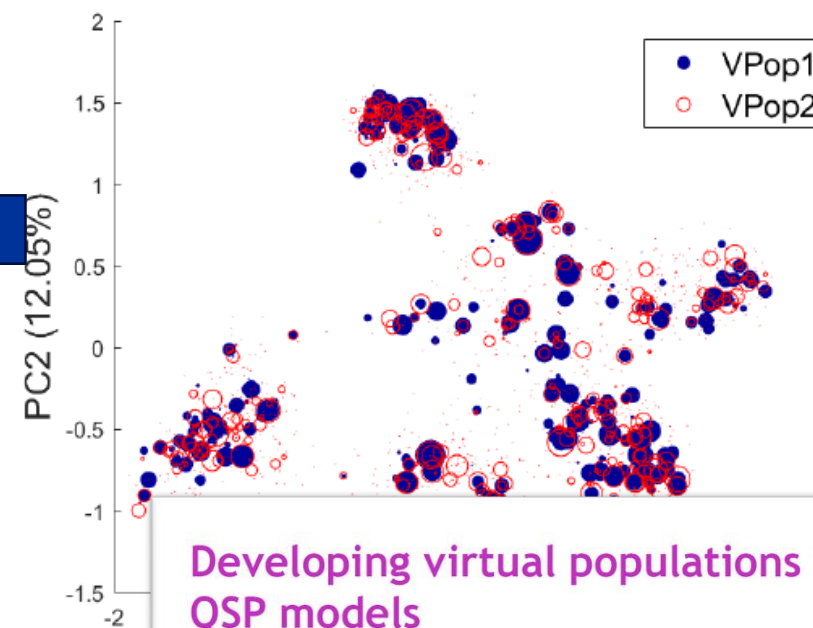


ISoP
INTERNATIONAL SOCIETY OF PHARMACOMETRICS

Credibility of QSP Virtual Populations in Rare Disease Drug Development

Mengdi Tao

Alternative Vpop



Developing virtual populations for QSP models

A workflow illustrated by an immune checkpoint inhibitor case study

Yili Qian on behalf of BMS QPDA team

Mengdi Tao (Sanofi), Yili Qian (BMS), Establishing QSP Virtual Population (VPOP) Credibility Assessment Workshop, May 19th, 2025, Rutgers University

11 The landscape of QSP modelling and Virtual Populations: from current to best practice



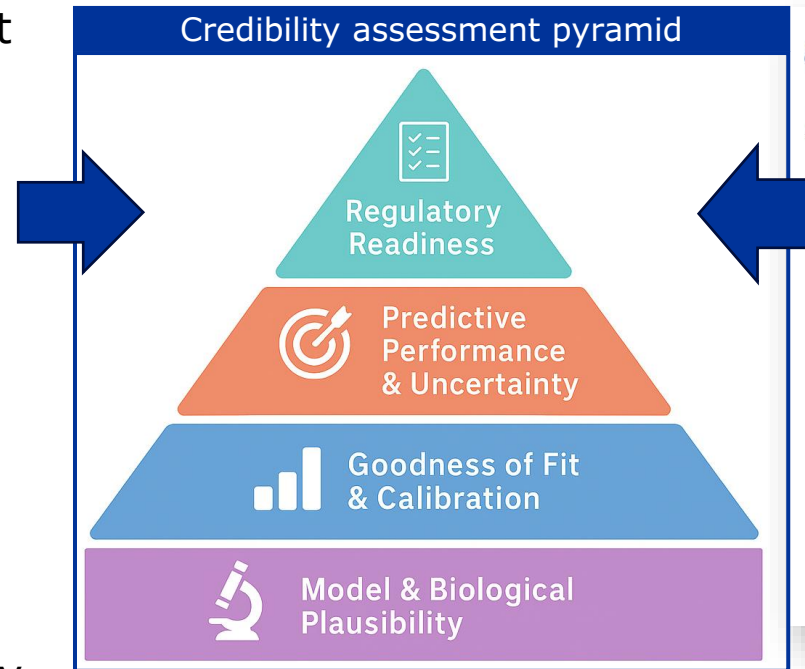
Regulatory readiness

QSP Vpop Assessment within Regulatory Use:

- No guidelines yet, however recent ICH M15 Guideline provides a framework.
- Key components:
 - Question of Interest
 - Context of Use
 - Model risk / impact
 - Data availability available for building vs. assessment

Vpop Validation:

- No "one size fits all"
- Dependent on calibration strategy
- Existent frameworks for assessment and reporting exist but need to take into account the biology as a driver and CoU



Overarching guideline for MIDD



INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL
REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

GENERAL PRINCIPLES FOR MODEL-INFORMED DRUG
DEVELOPMENT

M15

- Platform qualification will require cross-stakeholder collaboration, consensus on model and pooling data.
- Qualification of PBPK platforms can instruct on process and requirements

Key Takeaways

- **Diversity = Flexibility vs. Consistency = Standardization**
- **Maybe no standard workflows are possible but common themes & elements**
- **Working Group is working towards identifying more commonalities and more consistency**
 - **Consensus on terminology best practices**
 - **Reporting Best Practices**
 - **Credibility Assessment Best Practices**
 - Synthesize patterns from existing use cases using CoU frameworks
 - Evaluate areas of future growth for QSP for regulatory use
 - **Evaluate mature areas of QSP for regulatory use: cross-company TCE learnings and illustrative example toward qualification of QSP frameworks**

Acknowledgements

Cred Assessment Working Group:

- Blerta Shtylla (Chair, Pfizer),
- Steve Chang (Sims+),
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- Abhishek Gulati (Merck),
- Alexander Kulesza (ESQlabs),
- Alexander Ratushny (BMS),
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- Fulya Singh (Genmab),
- Monica Susilo (Genentech),
- Weirong Wang (JnJ),
- Susana Zaph (Sanofi)

ISoP QSP SIG Leadership Team

References

1. Allen RJ, Rieger TR, Musante CJ. Efficient Generation and Selection of Virtual Populations in Quantitative Systems Pharmacology Models. CPT Pharmacometrics Syst Pharmacol. 2016 Mar;5(3):140-6. doi: 10.1002/psp4.12063. Epub 2016 Mar 17. PMID: 27069777; PMCID: PMC4809626.
2. Cheng Y, Straube R, Alnaif AE, Huang L, Leil TA, Schmidt BJ. Virtual Populations for Quantitative Systems Pharmacology Models. Methods Mol Biol. 2022;2486:129-179. doi: 10.1007/978-1-0716-2265-0_8. PMID: 35437722.
3. Kaddi C, Tao M, Bergeler S, George K, Geerts H, van der Graaf PH, Batista JL, Foster M, Ortemann-Renon C, Zaher A, An Haack K, Zaph S. Quantitative Systems Pharmacology-Based Digital Twins Approach Supplements Clinical Trial Data for Enzyme Replacement Therapies in Pompe Disease. Clin Pharmacol Ther. 2025 Feb;117(2):579-588. doi: 10.1002/cpt.3498. Epub 2024 Dec 4. PMID: 39632463.
4. Susilo ME, Li CC, Gadkar K, Hernandez G, Huw LY, Jin JY, Yin S, Wei MC, Ramanujan S, Hosseini I. Systems-based digital twins to help characterize clinical dose-response and propose predictive biomarkers in a Phase I study of bispecific antibody, mosunetuzumab, in NHL. Clin Transl Sci. 2023 Jul;16(7):1134-1148. doi: 10.1111/cts.13501. Epub 2023 Mar 23. PMID: 36908269; PMCID: PMC10339700.
5. Poels KE, Elmeliegy M, Hibma J, Wang D, Musante CJ, Shtylla B. Leveraging quantitative systems pharmacology modeling for elranatamab regimen optimization in relapsed or refractory multiple myeloma. NPJ Syst Biol Appl. 2025 Sep 1;11(1):102. doi: 10.1038/s41540-025-00585-z. PMID: 40890126; PMCID: PMC12402305.
6. Androulakis IP. Towards a comprehensive assessment of QSP models: what would it take? J Pharmacokinet Pharmacodyn. 2024 Oct;51(5):521-531. doi: 10.1007/s10928-022-09820-0. Epub 2022 Aug 13. PMID: 35962928; PMCID: PMC9922790.
7. Cucurull-Sanchez L. An industry perspective on current QSP trends in drug development. J Pharmacokinet Pharmacodyn. 2024 Oct;51(5):511-520. doi: 10.1007/s10928-024-09905-y. Epub 2024 Mar 5. PMID: 38443663; PMCID: PMC11576823.
8. Weddell J, Gulati A, Yamada A. Recommendations for a standardized publication protocol for a QSP model. J Pharmacokinet Pharmacodyn. 2024 Oct;51(5):557-562. doi: 10.1007/s10928-024-09943-6. Epub 2024 Oct 10. PMID: 39390205.
9. Chan JR, Allen R, Boras B, Cabal A, Damian V, Gibbons FD, Gulati A, Hosseini I, Kearns JD, Saito R, Cucurull-Sanchez L, Selimkhanov J, Stein AM, Umehara K, Wang G, Wang W, Neves-Zaph S. Current practices for QSP model assessment: an IQ consortium survey. J Pharmacokinet Pharmacodyn. 2024 Oct;51(5):543-555. doi: 10.1007/s10928-022-09811-1. Epub 2022 Aug 11. PMID: 35953664; PMCID: PMC9371373.
10. [QSP-model based assessment of mechanistic similarity of disease and response to olipudase alfa between pediatric and adult Acid Sphingomyelinase Deficiency \(ASMD\) patients](#)
11. [pfizer-opensource/integrated-qsp-vpop-onco-efficacy-CPT-PSP: Code for the manuscript "An integrated quantitative systems pharmacology virtual population approach for calibration with oncology efficacy endpoints."](#)
12. <https://github.com/BMSQSP/QSPToolbox>
13. <https://github.com/openPfizer/vpop-gen>