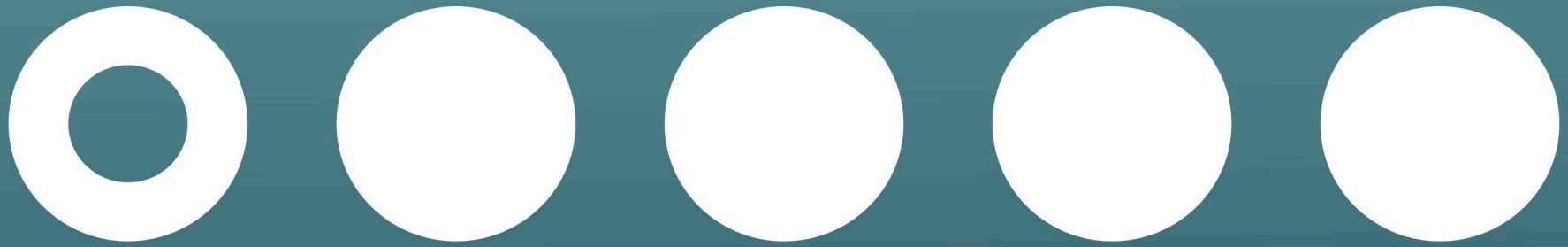
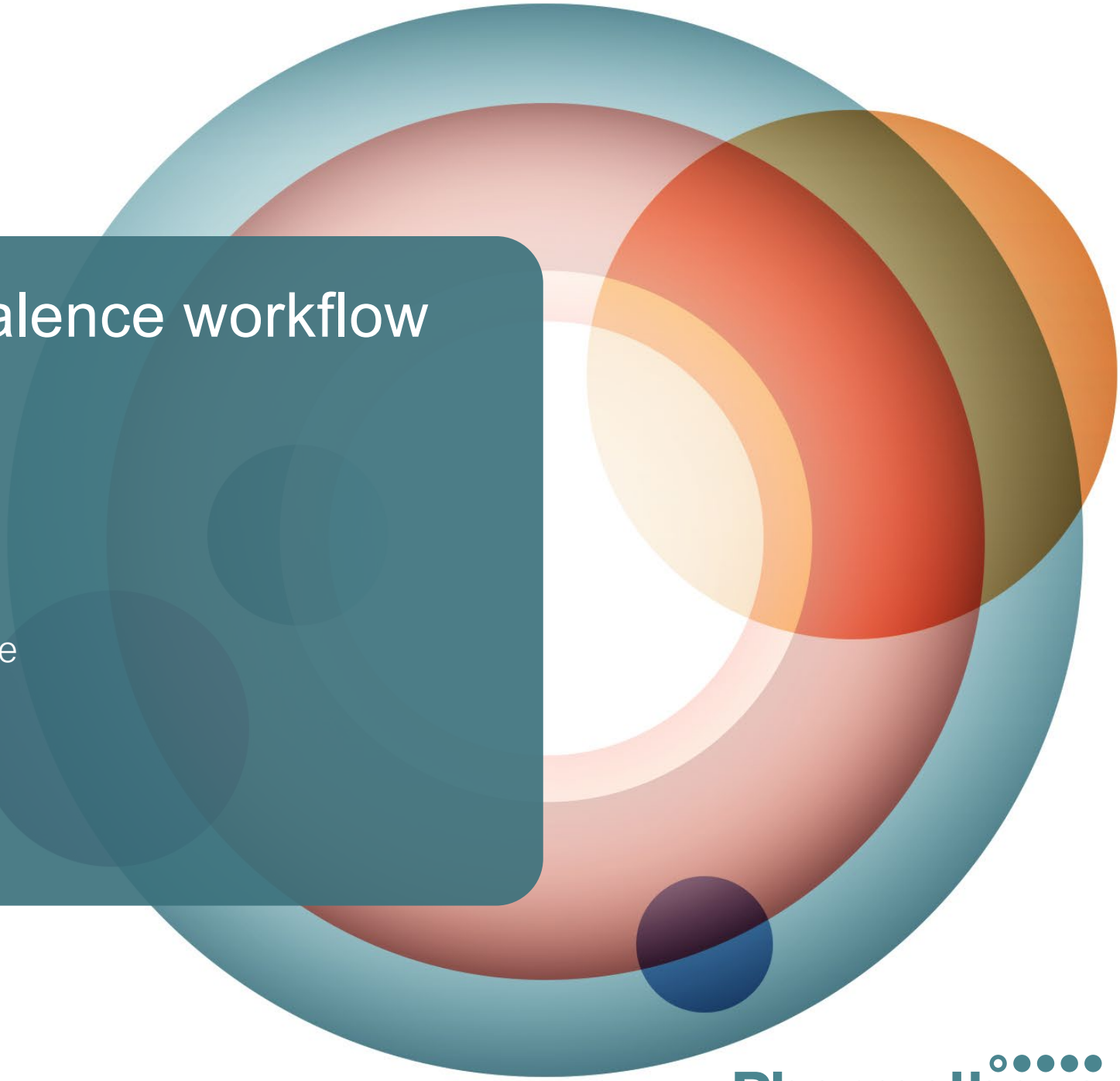


Pharmetheus

Virtual bioequivalence workflow

Erik Sjögren, Moriah Pellowe
Pharmetheus

PAGE workshop
June 28, 2022



Pharmetheus

US FDA grant U01FD006549: Virtual bioequivalence (VBE) workflow

- Objective: Develop platform within Open Systems Pharmacology framework for VBE assessment

- Associate MIDD consultant:
  - Moriah Pellowe (previously post-doctoral fellow in Edginton lab)

- Principal Investigators:
  - Michael Neely – Children's Hospital Los Angeles
  - Andrea Edginton – University of Waterloo
  - Jörg Lippert – Bayer

- Project officer:
  - Eleftheria Tsakalozou – US FDA

US FDA disclaimer

The views expressed in this presentation do not reflect the official policies of the U.S. Food and Drug Administration or the U.S. Department of Health and Human Services; nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.

Outline

- Background
  - Bioequivalence (BE)
  - Virtual bioequivalence (VBE)
  - In vitro-in vivo relationship (IVIVR)
- VBE workflow overview (with case study)
  - Requirements – PK-Sim
  - Capture posterior distributions - NPOD
  - Generate virtual population and PK profiles – PK-Sim
  - Clinical trial simulator – CTS
- Applications
- Acknowledgements

Bioequivalence (BE)

- A test formulation is **bioequivalent** to a reference formulation if …

  "The rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses."

  (Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA Guidance for Industry – FDA draft guidance)

- Same active pharmaceutical ingredient (API) at same dose
- Similar rate and extent of absorption, i.e. confidence intervals of the ratio of Cmax and AUC is within 0.8-1.25

Virtual bioequivalence (VBE)

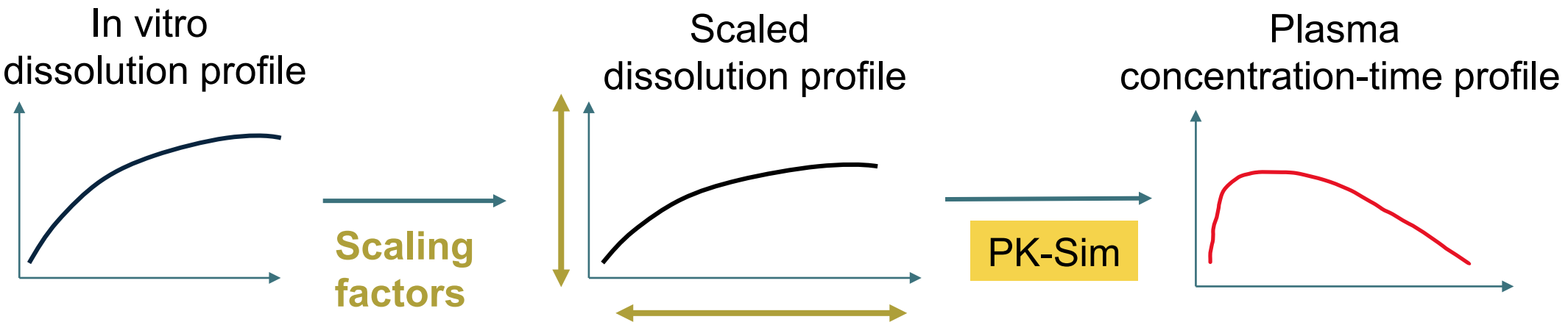
- Bioequivalence is important in drug development
  - Generics
  - Formulation changes
  - Manufacturing changes

- Clinical trials are costly in terms of time and money
- Some clinical trials for bioequivalence are not possible
  - An insufficient number of participants with rare diseases
  - Pediatric populations
  - Anti-drug antibodies for biologics wouldn't allow for crossover studies

- Virtual bioequivalence is a tool that can be used to identify potential candidates for bioequivalence to be tested in a clinical trial

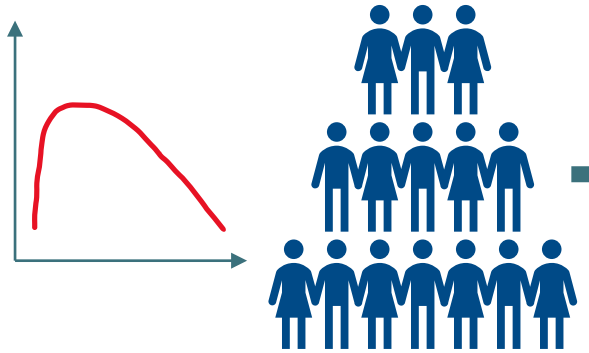
In vitro-in vivo relationship (IVIVR)

- Need to find a relationship between the *in vitro* dissolution profiles and the *in vivo* absorption of the drug
- This workflow utilizes dissolution scaling factors in MoBi to do this



VBE workflow overview

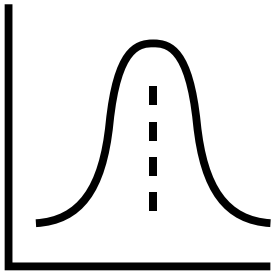
Study population and observed PK profiles



NPOD

PK-Sim

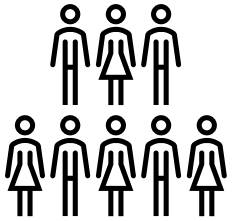
Distribution capturing IIV



- IVIVR (absorption)
- Organism-specific parameters (clearance)

PK-Sim

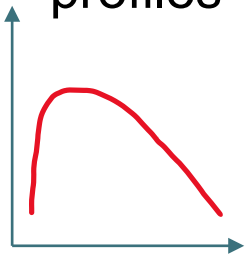
Initial virtual population



Updated virtual population

PK-Sim

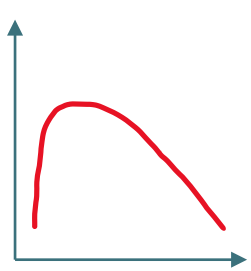
Simulated PK profiles

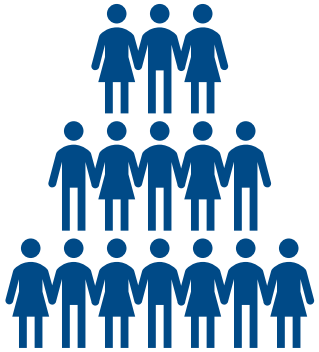


CTS

VBE workflow overview

Study population and observed PK profiles





PK-Sim

Requirements – PK-Sim

- PK-Sim model for molecule (.pkml)
  - Model for reference formulation
  - Model for test formulation
- Sensitive model parameters to capture IIV

- Observed plasma concentration-time profiles for study population
- Study population demographics (population, sex, weight, height, age)

Case study: Bupropion

Disclaimer: Bupropion is used as a test model to demonstrate the workflow

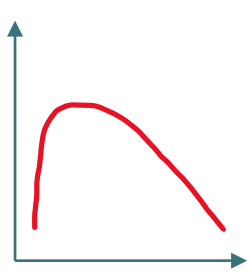
- Bupropion PK-Sim models:
  - Reference: SR 150 mg
  - Test: XL 150 mg
  - Sensitive parameters: Enzyme concentration, dissolution scaling factors
- Plasma concentration-time profiles for 32 individuals
- Study population demographics (sex, population, weight, height)

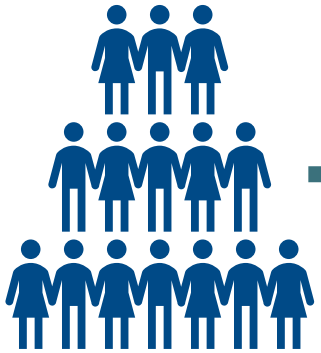
Reference:

Connarn JN, Flowers S, Kelly M, Luo R, Ward KM, Harrington G, Moncion I, Kamali M, McInnis M, Feng MR, Ellingrod V, Babiskin A, Zhang X, Sun D. Pharmacokinetics and Pharmacogenomics of Bupropion in Three Different Formulations with Different Release Kinetics in Healthy Human Volunteers. AAPS J. 2017 Sep;19(5):1513-1522. doi: 10.1208/s12248-017-0102-8. Epub 2017 Jul 6. PMID: 28685396.

VBE workflow overview

Study population and observed PK profiles

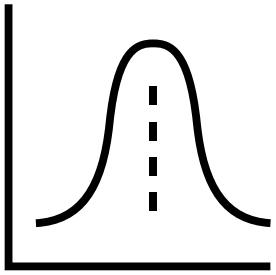




NPOD

PK-Sim

Distribution capturing IIV



- IVIVR (absorption)
- Organism-specific parameters (clearance)

Capturing posterior distributions - NPOD

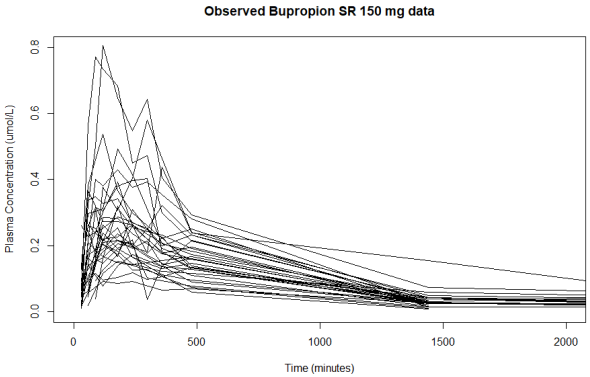
- Initial virtual population consists of “digital twins” of study population based on demographics
- Parameter ranges are specified for sensitive parameters

- Input: reference formulation model, observed data, parameter ranges, study individuals
- Output:
  - Posterior distributions (support points and weights)
    - Capable of capturing non-normal distributions, e.g. poor and extensive metabolizers
  - Correlation matrix between parameters and population demographics (e.g. weight, height)

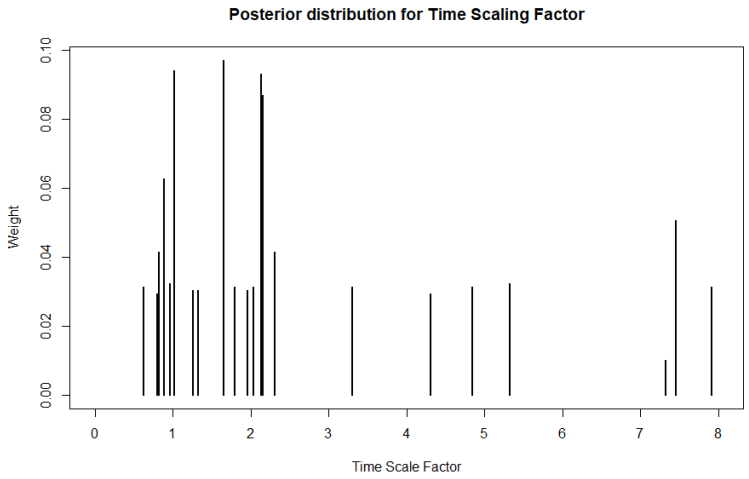
Case study: Bupropion

Reference: Connarn et al, 2017

- Reference bupropion model: SR 150 mg
- Parameter ranges are specified for sensitive parameters to be fit
  - Time scaling factor on dissolution profile (i.e. x-axis factor)
  - Fraction (dose) scaling factor on dissolution profile (i.e. y-axis factor)
  - Enzyme reference concentration



ID	Sex	Populatio	Weight (k	Height (cm)
1	Female	European	72.7	167.64
2	Female	European	84.4	162.56
3	Male	BlackAme	73.4	172.72
4	Male	MexicanA	79.8	167.64
5	Female	European	91.1	181.61
6	Female	Asian	74	172.72
7	Male	Asian	77.7	170.18
8	Female	European	73.5	167.64
9	Male	European	80.6	187.96
10	Male	European	94.7	170.18

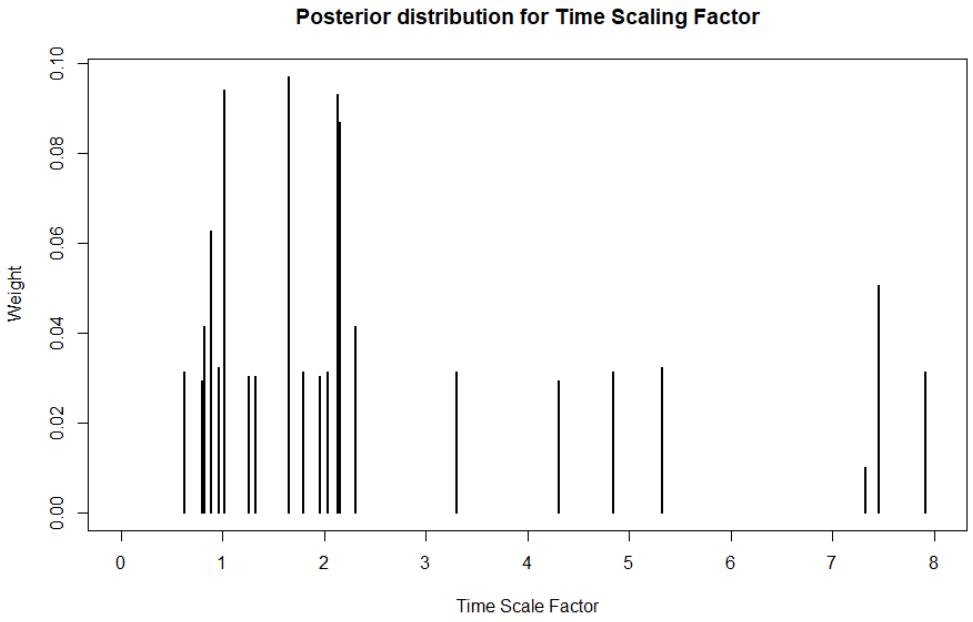



```
> corr_matrix
             theta1     theta2      theta3      Weight      Height
theta1  1.00000000  0.5655141 -0.64178739 -0.30277260 -0.09624631
theta2  0.56551415  1.0000000 -0.39004246 -0.23190258 -0.13329034
theta3 -0.64178739 -0.3900425  1.00000000  0.06232417  0.13168306
Weight -0.30277260 -0.2319026  0.06232417  1.00000000  0.38472801
Height -0.09624631 -0.1332903  0.13168306  0.38472801  1.00000000
```

Case study: Bupropion

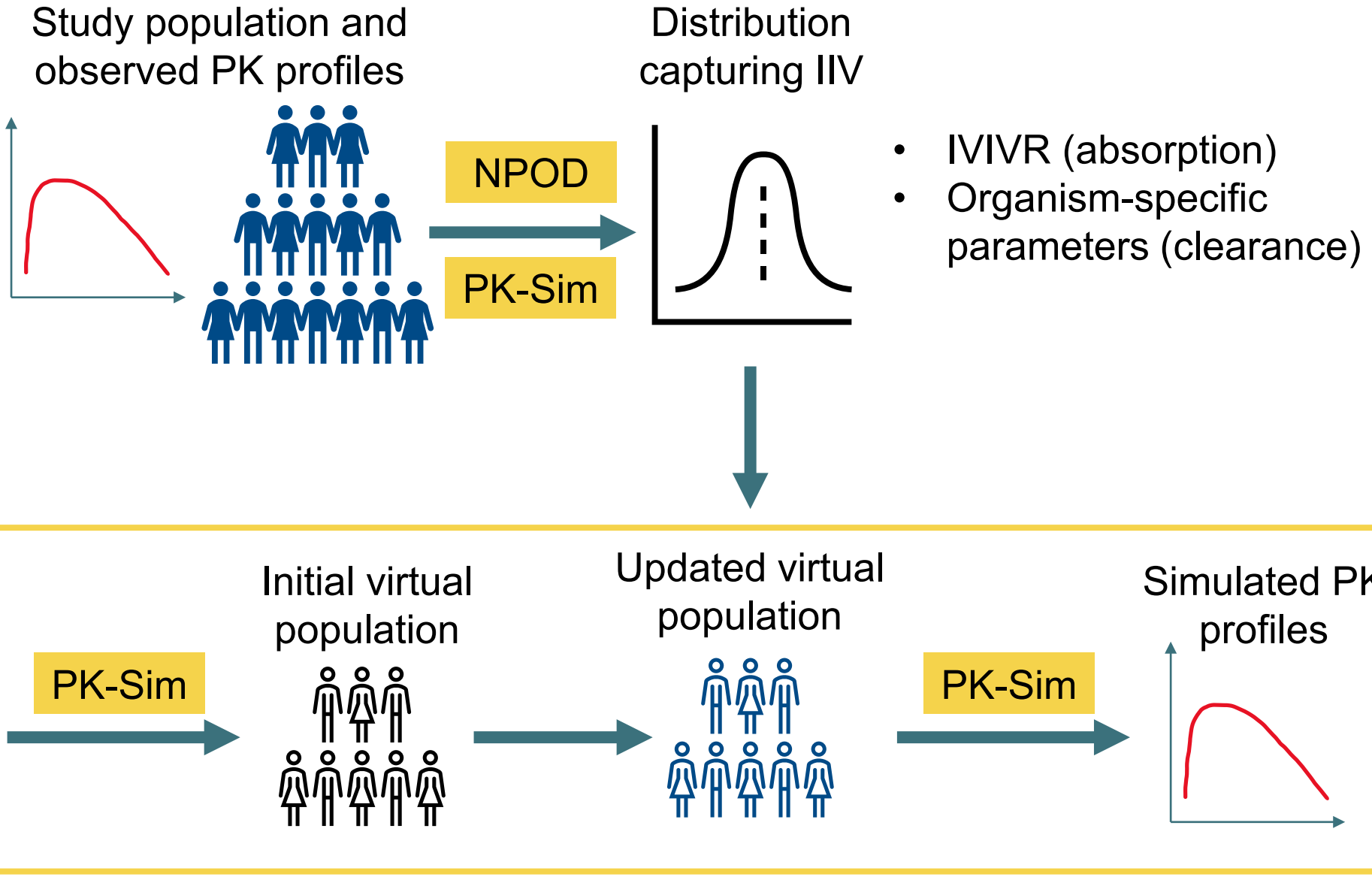
- A reference population of 1000 individuals is generated that maintains the captured correlations from the non-parametric population algorithm

	theta1	theta2	theta3	weight	height
1	1.2622520	137.60412	813.9782	107.93443	19.36761
2	0.8930129	43.19603	820.1831	61.03642	17.51424
3	1.6527643	47.60304	678.9087	99.33016	17.54653
4	2.1600338	62.21984	820.1831	86.89934	17.39655
5	2.0332647	110.45191	821.0817	55.76694	17.20736
6	0.8022292	55.45703	841.1291	78.72036	17.00976
7	2.3100450	100.05055	820.1831	62.96131	16.68466
8	0.8930129	59.12914	946.9103	61.52944	18.16568
9	4.3044085	58.06531	933.7260	55.49252	17.55697
10	1.9635224	43.19603	933.7260	57.89853	18.83575




```
> corr_matrix
            theta1     theta2      theta3      weight      Height
theta1  1.00000000  0.5655141 -0.64178739 -0.30277260 -0.09624631
theta2  0.56551415  1.0000000 -0.39004246 -0.23190258 -0.13329034
theta3 -0.64178739 -0.3900425  1.00000000  0.06232417  0.13168306
Weight -0.30277260 -0.2319026  0.06232417  1.00000000  0.38472801
Height -0.09624631 -0.1332903  0.13168306  0.38472801  1.00000000
```

VBE workflow overview



Generate virtual population and PK profiles – PK-Sim

- OSPsuite is used to generate a virtual population
- The virtual population parameters are updated based on the reference population
- PK-Sim is used to generate the PK profiles for both the reference and test formulations

Case study: Buproprion

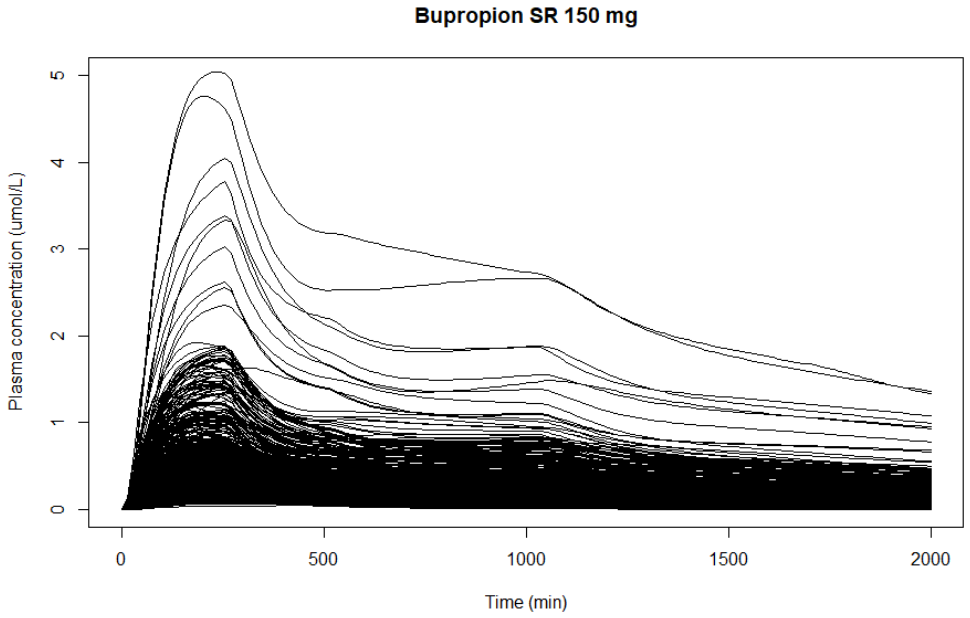
- A virtual population of 1000 individuals is generated
- Virtual individuals are compared to reference population and the appropriate parameter values are updated

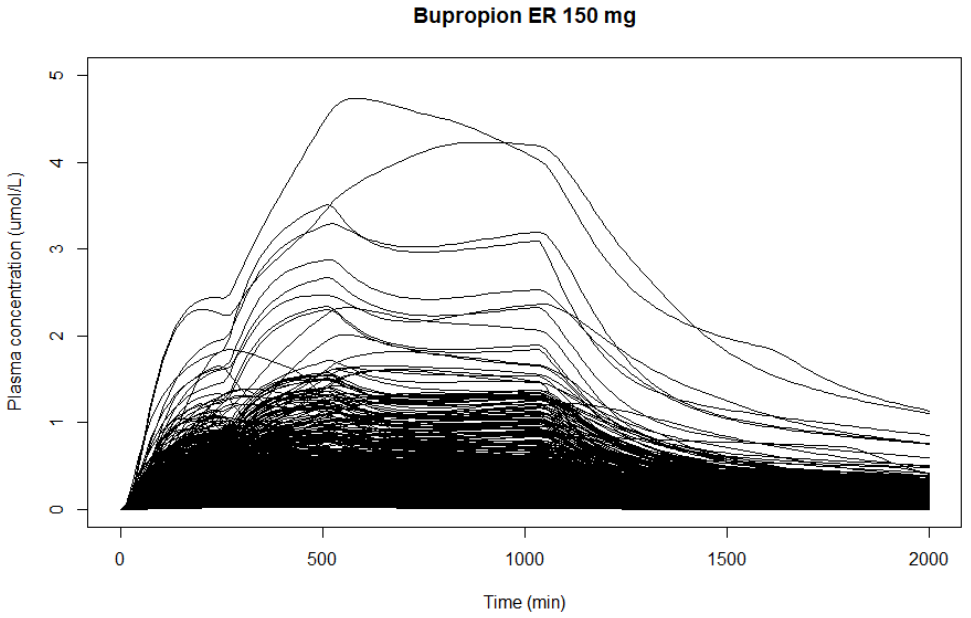
	theta1	theta2	theta3	weight	height
1	1.2622520	137.60412	813.9782	107.93443	19.36761
2	0.8930129	43.19603	820.1831	61.03642	17.51424
3	1.6527643	47.60304	678.9087	99.33016	17.54653
4	2.1600338	62.21984	820.1831	86.89934	17.39655
5	2.0332647	110.45191	821.0817	55.76694	17.20736
6	0.8022292	55.45703	841.1291	78.72036	17.00976
7	2.3100450	100.05055	820.1831	62.96131	16.68466
8	0.8930129	59.12914	946.9103	61.52944	18.16568
9	4.3044085	58.06531	933.7260	55.49252	17.55697
10	1.9635224	43.19603	933.7260	57.89853	18.83575

IndividualId	Gender	Population	Organism|Weight	Organism|Height	Applications|PO	Applications|PO 15	Liver and Intestina
0	MALE	European_ICRP_2002	69.67197648	17.34863337	1.652764258	43.1960325	966.1631612
1	MALE	European_ICRP_2002	80.66367394	17.31971653	0.893012886	55.45703163	946.9102584
2	MALE	European_ICRP_2002	11.6418776	7.739270429	4.304408454	137.6041153	678.9087472
3	MALE	European_ICRP_2002	73.25415791	17.61428916	0.802229246	43.1960325	986.9442911
4	MALE	European_ICRP_2002	86.73495227	17.28527499	2.1600338	62.21983888	820.1831479
5	MALE	European_ICRP_2002	67.65264677	17.44606382	2.138830071	100.0505509	373.7770325
6	MALE	European_ICRP_2002	63.98918339	16.50535396	7.454465816	110.4519128	886.9854164
7	MALE	European_ICRP_2002	13.79027881	9.18601242	4.304408454	137.6041153	678.9087472
8	MALE	European_ICRP_2002	62.59547048	16.41364181	7.454465816	82.09933596	670.7724672
9	MALE	European_ICRP_2002	61.88576613	17.19057429	4.839407277	82.09933596	813.9781987
10	MALE	European_ICRP_2002	55.92556148	15.07635357	1.963522405	41.58242253	820.1118292

Case study: Buproprion

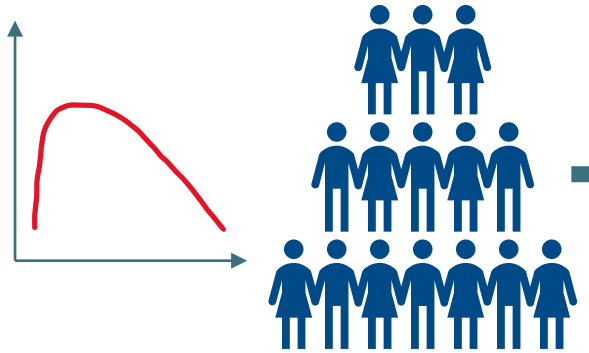
- Plasma concentration-time profiles are generated for the virtual population for the reference formulation and for the test formulation





VBE workflow overview

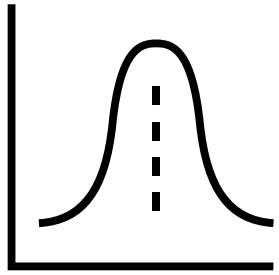
Study population and observed PK profiles



NPOD

PK-Sim

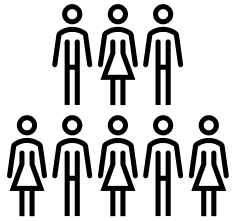
Distribution capturing IIV



- IVIVR (absorption)
- Organism-specific parameters (clearance)

PK-Sim

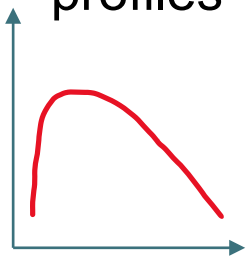
Initial virtual population



Updated virtual population

PK-Sim

Simulated PK profiles



CTS

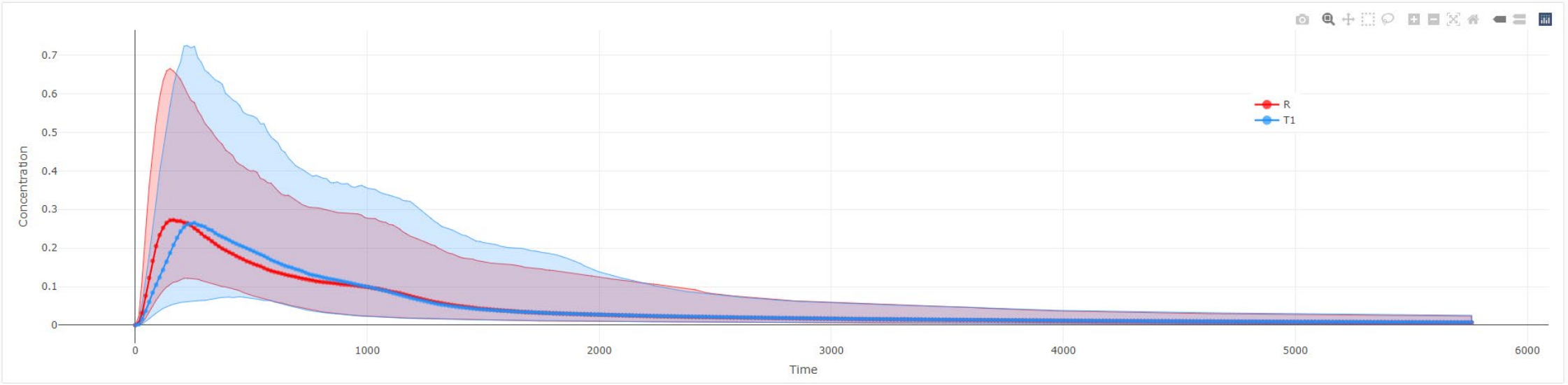
Clinical trial simulator - CTS

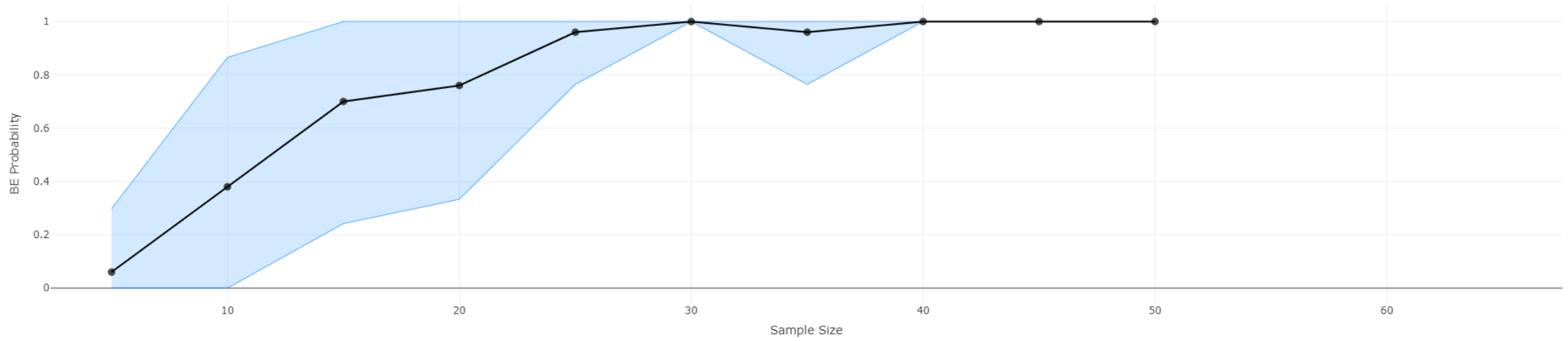
- Input: Simulated plasma concentration-time profiles for two formulations (reference and test)
- CTS calculates the summary statistics (AUC, Cmax, etc.)
- Virtual bioequivalence is evaluated from these summary statistics

- Multiple scenarios possible:
  - Independent studies with no cross-over, i.e. different populations, different formulations
  - Cross-over, no replication (AB)
  - ~~Cross-over with partial or full replication (ABA, BAB, ABAB) with IOV~~

Clinical trial simulator - CTS

BE Report | Simulated Data | Parallel Design | Cross-over Design | Replicate Design





Applications

- Generic drug development
- Predicting establishment of bioequivalence for a test formulation
- Creating a “dissolution safe space”
- Optimizing clinical trial design

Acknowledgements

- Moriah Pellowe (Pharmetheus, UW)
- Andrea Edginton (UW)
  - Abdullah Hamedeh
  - Cindy Hoi Ting Yeung
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  - Julian Oltalvaro
  - Walter Yamada
  - Alona Kryshchenko (California State University Channel Islands)
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  - Juri Solodenko
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