Virtual bioequivalence workflow

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FDA grant U01FD006549: Virtual bioequivalence (VBE) workflow

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- Scientific officer:
  - Eleftheria Tsakalozou
- Objective: Develop platform within OSP framework for VBE assessment

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  - Reference: in vitro dissolution profile + individual PK data
  - Test: in vitro dissolution profile

Build API oral model with reference IV and solution/IR data

Identify relevant physiologic parameters that affect PK using sensitivity and uncertainty analyses

Identify posterior distributions based on individual PK data using “digital twins”

Generate a virtual population that captures the measured variability

Simulate individual plasma concentration vs time profiles for reference and test

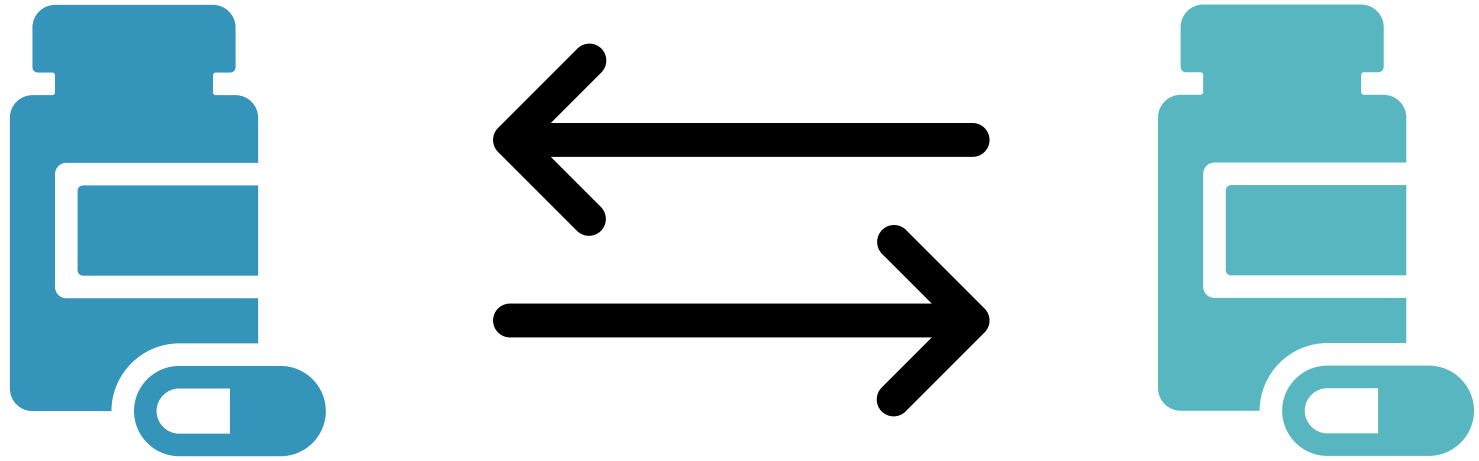
Use non-compartmental analysis to get AUC, Cmax and Tmax and complete BE statistics appropriate for study design

Optimize clinical trial design (e.g number of participants and sampling)

Applications

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

- Risk assessment
  - Generic drug development
  - Pre-approval formulation changes
  - Scale-up and post-approval changes



Virtual bioequivalence workflow

Building an oral PK-Sim model

- Physicochemical properties of the drug
- Known physiological processes

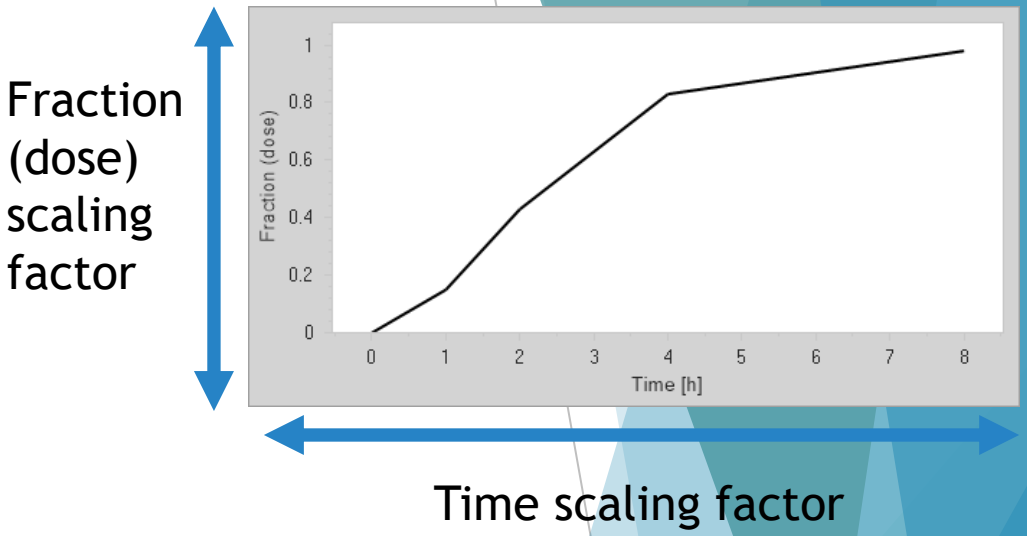
- IV data informs systemic parameters of disposition
- Solution/IR data informs systemic parameters of absorption
- We are assuming that the plasma concentration-time profiles are sensitive to formulation input (e.g. dissolution profile)

- At the end of this step, we have…
  - PBPK model that describes systemic disposition and absorption of API

Establishing an in-vitro-in-vivo relationship (IVIVR)

- Mechanistic:
  Formulation parameters (e.g. particle size distribution)
- In the absence of *a priori* knowledge:
  Dissolution scaling factors

- Reference data (formulation input and plasma concentration-time profiles) is used to calibrate the IVIVR
- We assume that the IVIVR applies to test formulations
  - Ideally, the test formulation is similar in excipients and release mechanisms compared to the reference formulation



Case study: Bupropion

- Note: Bupropion is just a pilot model used to demonstrate a crossover virtual bioequivalence assessment

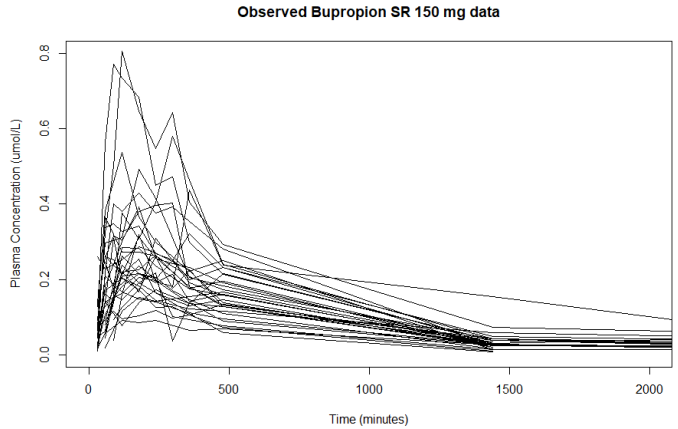
- Bupropion PK-Sim models:
  - Reference: SR 150 mg
  - Test: XL 150 mg
  - Sensitive parameters:
    - Enzyme reference concentration, Dissolution scaling factors
- Plasma concentration-time profiles for 32 individuals
- Study population demographics (sex, population, weight, height)

Capturing posterior distributions – Non-parametric optimal design (NPOD)

- Study individuals are recreated as “digital twins” in PK-Sim using demographic data available
- Parameter ranges are specified for sensitive parameters to be fit

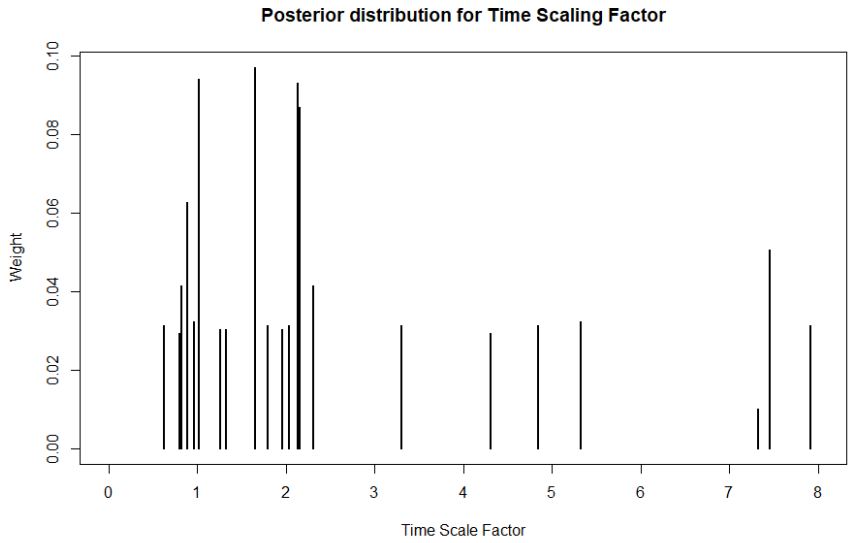
- Input: API oral model, observed data, parameter ranges, study individuals
- Output:
  - Posterior distributions (support points and weights)
    - Capable of capturing non-normal distributions, e.g. poor and extensive metabolizers
  - Correlation matrix between parameters and population demographics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

Case study: Bupropion



- Reference formulation: SR 150 mg
- Parameter ranges are specified for sensitive parameters to be fit
  - Time scaling factor on dissolution profile (i.e. x-axis) – [0,10]
  - Fraction (dose) scaling factor on dissolution profile (i.e. y-axis) – [0,1000]
  - Enzyme reference concentration – [0,1000]

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

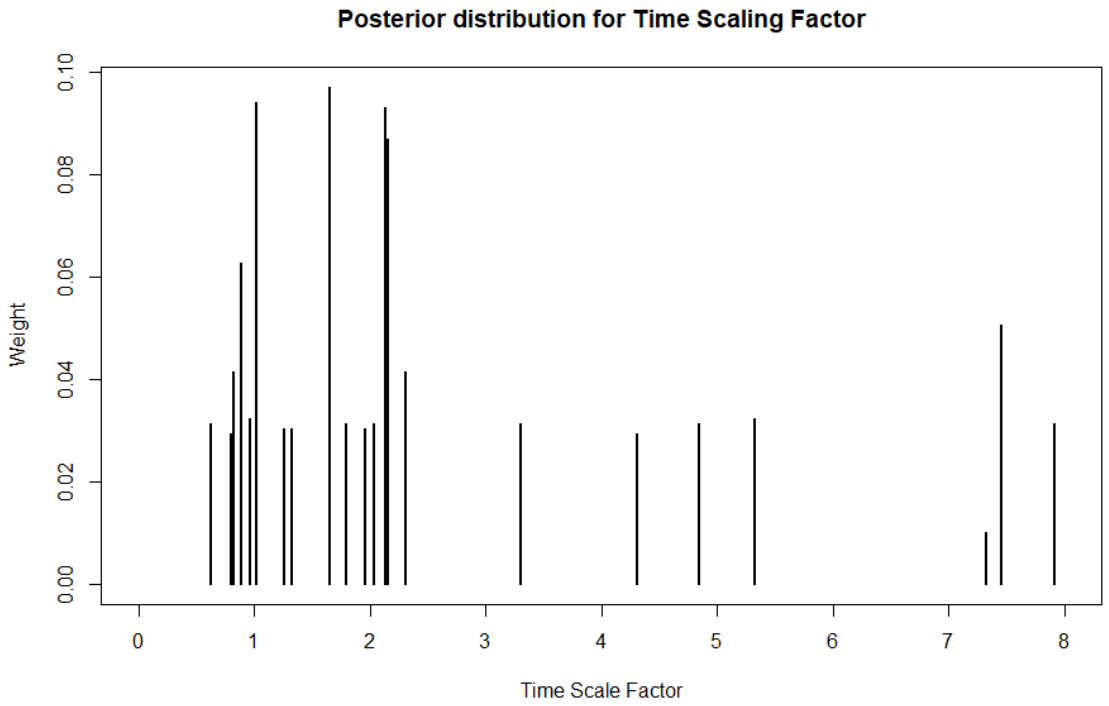



```
> corr_matrix
             theta1     theta2      theta3      Weight      Height
theta1  1.00000000  0.5655141 -0.64178739 -0.30277260 -0.09624631
theta2  0.56551415  1.0000000 -0.39004246 -0.23190258 -0.13329034
theta3 -0.64178739 -0.3900425  1.00000000  0.06232417  0.13168306
Weight -0.30277260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

Case study: Bupropion

- A reference table of 1000 parameter sets 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

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weight -0.30277260 -0.2319026  0.06232417  1.00000000  0.38472801
Height -0.09624631 -0.1332903  0.13168306  0.38472801  1.00000000
```

Generate virtual population and PK profiles

- OSP suite R toolbox is used to generate a virtual population
- The virtual population is updated based on the reference table
- PK-Sim is used to generate the PK profiles for both the reference and test formulations

Case study: Bupropion

- A virtual population of 1000 individuals is generated
- Virtual individuals are compared to reference table 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
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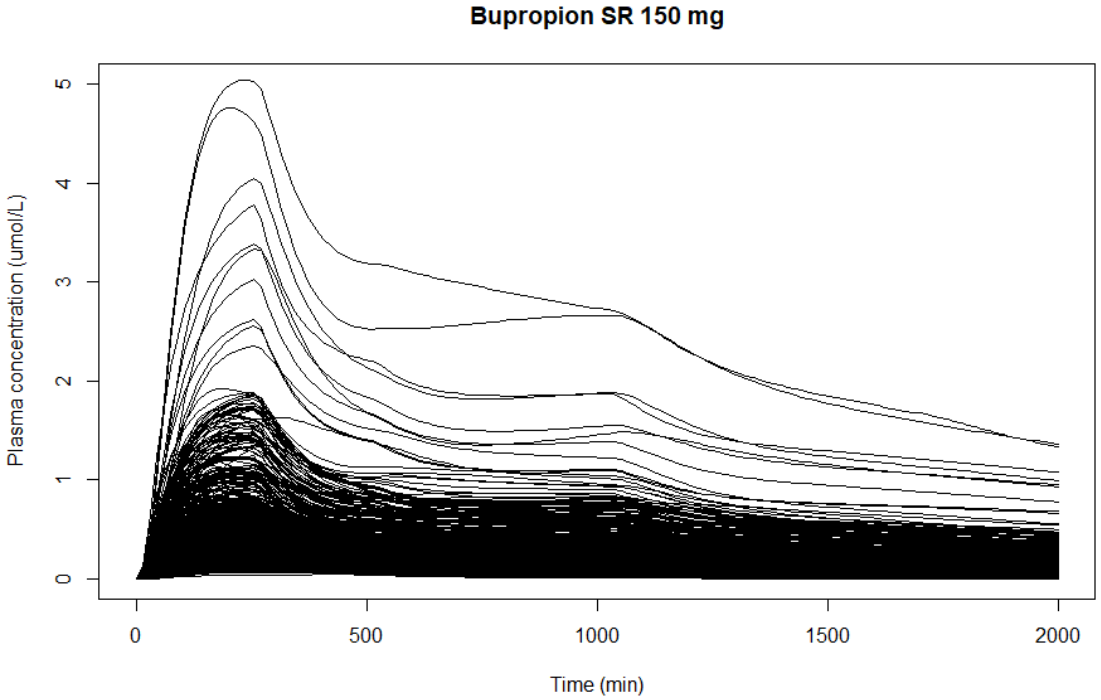
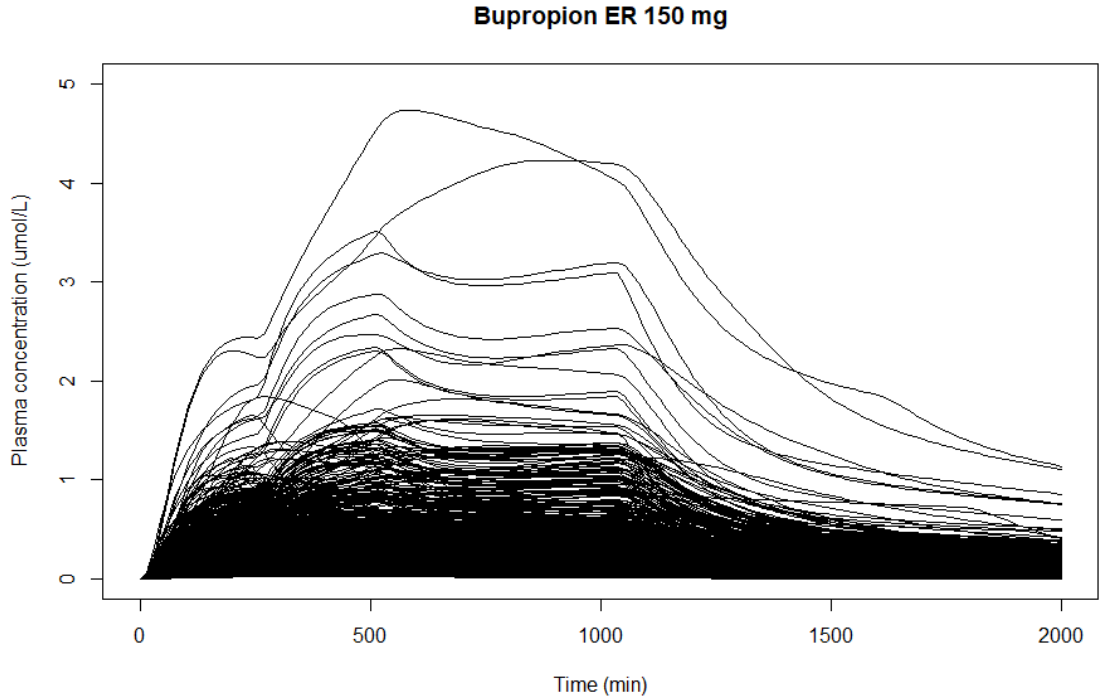
IndividualId	Gender	Population	Organism|Weight	Organism|Height	Applications|PO	Applications|PO 15	Liver and Intestina
0	MALE	European_ICRP_2002	69.67197648	17.34863337	1.652764258	43.1960325	966.1631612
1	MALE	European_ICRP_2002	80.66367394	17.31971653	0.893012886	55.45703163	946.9102584
2	MALE	European_ICRP_2002	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: Bupropion

- Plasma concentration-time profiles are generated for the virtual population for the reference formulation and for the test formulation
- We assume that the IVIVR applies to test formulations

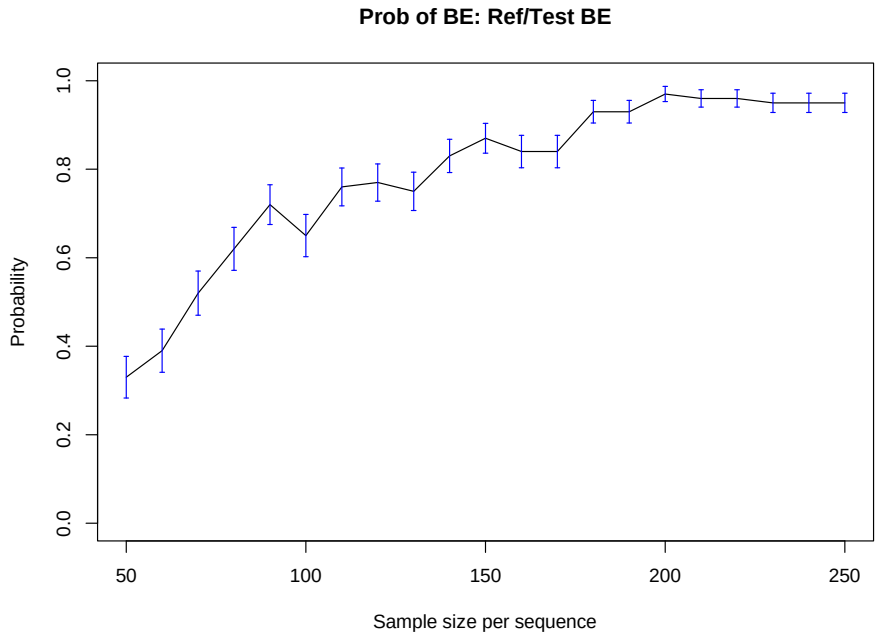


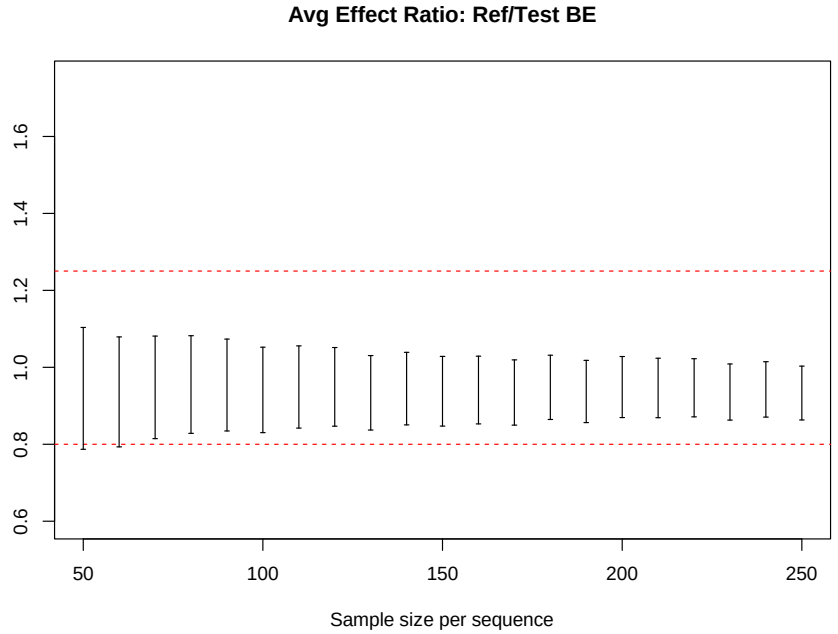


Clinical trial simulator (CTS) – *in progress*

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

- Multiple scenarios possible:
  - Parallel, i.e. different populations, different formulations
  - Crossover, no replication (AB)
  - Crossover with partial or full replication (e.g. TTR, TTRR) with IOV





Inter-occasion variability (IOV) – *in progress*

- **Mechanistic approach**
  - Identify physiological parameters that are affected by IOV for given API
  - Use NPOD to identify posterior distributions and correlations for these parameters (in addition to other fitted parameters)
  - Sample from these distributions during the generation of the virtual populations
- IOV is incorporated when the virtual populations are generated, i.e. before plasma concentration-time profiles are simulated

Applications

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

- Risk assessment
  - Generic drug development
  - Pre-/post-approval formulation changes
  - Scale-up and post-approval changes

Deliverables related to FDA grant

- Virtual bioequivalence workflow – R package
  - PK-Sim
  - OSP Suite R toolbox (ospsuite, will be discussed in Session 4) (https://github.com/Open-Systems-Pharmacology/OSPSuite-R)
  - Non-parametric optimal design (NPOD)
  - Clinical trial simulator (CTS)
- Mechanistic absorption models (will be discussed in Session 4)
  - Dermal model (https://github.com/Open-Systems-Pharmacology/Skin-permeation-model)
  - Inhalation model (https://github.com/Open-Systems-Pharmacology/Inhalation-model)
- The VBE workflow will be available on the Open Systems Pharmacology Github page (https://github.com/Open-Systems-Pharmacology)
  - Current goal: August 2021

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  - Cindy Hoi Ting Yeung
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