Strengths and Weaknesses of Population PK Analyses for the Assessment of Bioequivalence of Complex and Locally Acting Products

Leveraging Quantitative Methods and Modeling
to Modernize Generic Drug Development and Review Workshop
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10903 New Hampshire Av., Silver Springs, MD, USA
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Murray P. Ducharme, PharmD, FCCP, FCP
President and CEO, Learn and Confirm Inc.
And, Professeur Associé, Faculté de Pharmacie, University of Montreal, Montreal, Canada
And, Visiting Professor, Faculty of Pharmacy, Rhodes University, South Africa

Population PK in BE

Plan

- Background
- Estimating BE: Available methods and their limitations
- Utility and weaknesses of Population PK for BE
  - BE studies conducted in patients
  - Complex PK
    - Endogenous products
    - Iron products
  - « Non identical » APIs
    - Biosimilars
    - Iron products
  - Locally acting products
    - Topical products (Acyclovir cream)
    - Inhalers
- Conclusions

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Only 2 examples presented today due to time constraints

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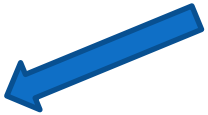
How is "Bioequivalence" or "Therapeutic Interchangeability" assessed for US FDA / EMA / HC for most products?

Problem with complicated drugs such as iron products, sevelamer, Biosimilars,…



- Pharmaceutical Equivalence
  - *Identical amounts of identical medical ingredients, comparable dosage forms*
- Therapeutic Equivalence / Bioequivalence
  - *Rate and Extent at which the active ingredient or therapeutic ingredient is absorbed from a drug product and becomes available at the site of drug action (21CFR 505(j)(8))*

    (By typical order of preference: PK studies, PD studies, Clinical trials, in vitro studies)
- Same route of administration
- Same conditions of use

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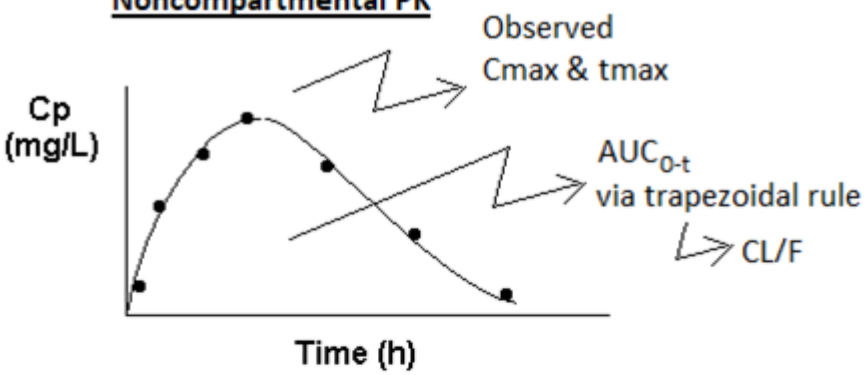
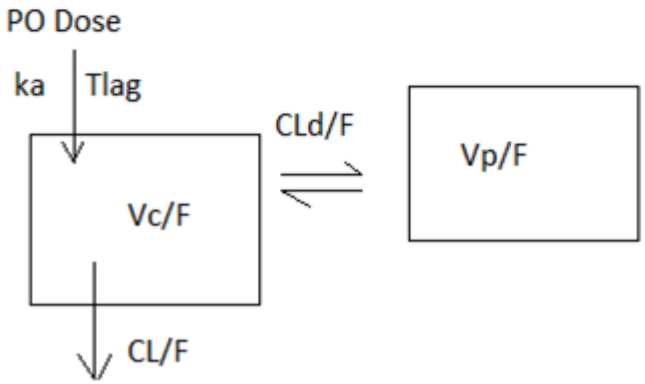
Population PK in BE

PK Methods

Noncompartmental PK

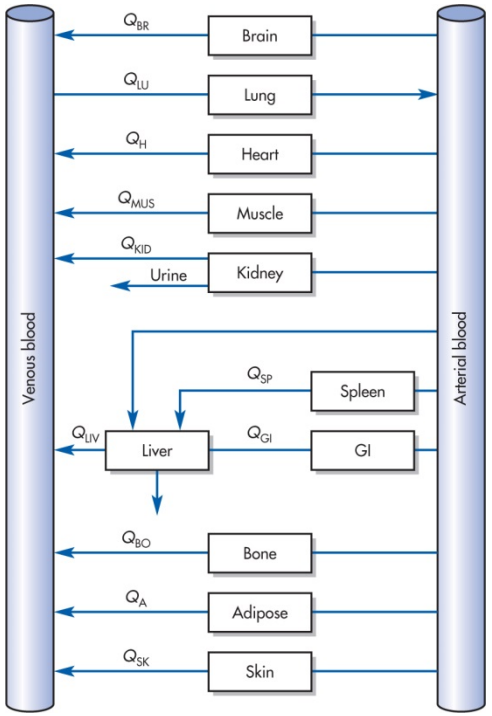


Population PK



Residual variability

PB PK



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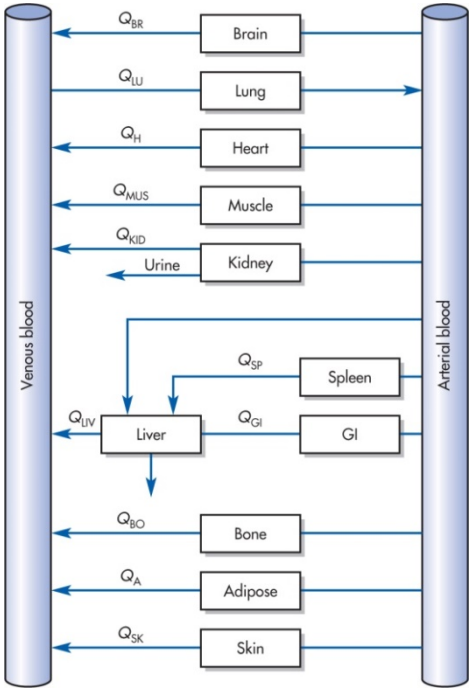
Population PK in BE

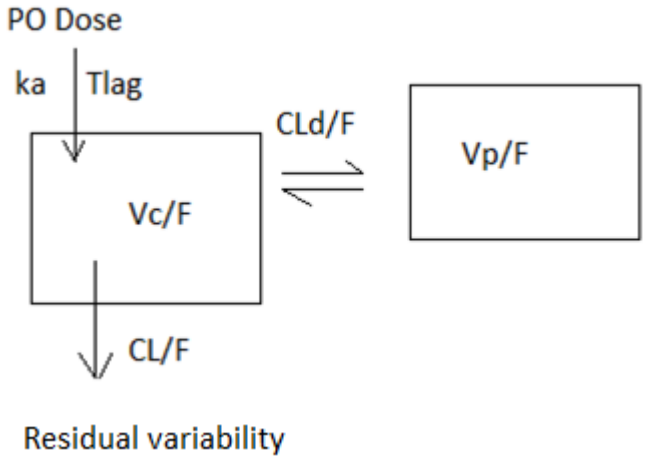
PK Methods



PB PK

"Bottom-Up" approach

- When no data is available
- Complicated model ("not identifiable") with most or all parameters fixed or assumed



Pop PK

"Top-Down" approach

- Parameters are fitted to the data, so data is needed
- Model needs to be "identifiable"

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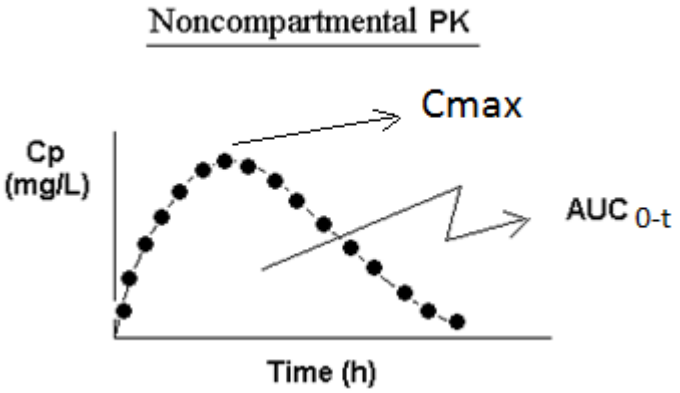
Population PK in BE

PK Methods

Noncompartmental approach or "Observed" PK approach in BE

•Simplest and Best approach ("reference approach")
- •Single dose design
- •Healthy volunteers
- •> 12 concentrations per profile
- •LLOQ < 5% of Cmax



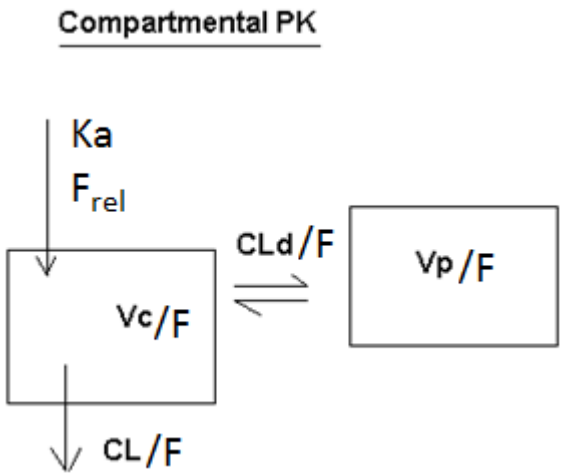
>90-95% of PK studies

Limitations

•Endogenous substances with unstable baseline, feedback or high baseline values versus Cmax
•Substances exhibiting non linearity
•Products with API that cannot be fully characterized as being"Identical"
•Complicated Dosing in patients (nor SD nor SS, insufficient washout,…)

Population PK approach in BE

- Can help distinguish between formulation and API similarities/differences
- Can be a mechanistic model that takes into account an unstable or large baseline effect
- Can take into consideration nonlinearity whether in elimination (not formulation specific) or release (formulation specific)
- Does not need SD or SS dosing



Limitations

•Complex analysis that needs to be redone for verification by regulators

•Still an “art” type analysis where there is no cookbook recipe, and where different models and assumptions will lead to different results

•Is more (too much?) discriminative than NCPT/Observed PK approach, as “rate” differences are compared (Ka) instead of mixture of rate&Extent (Cmax)

Population PK in BE

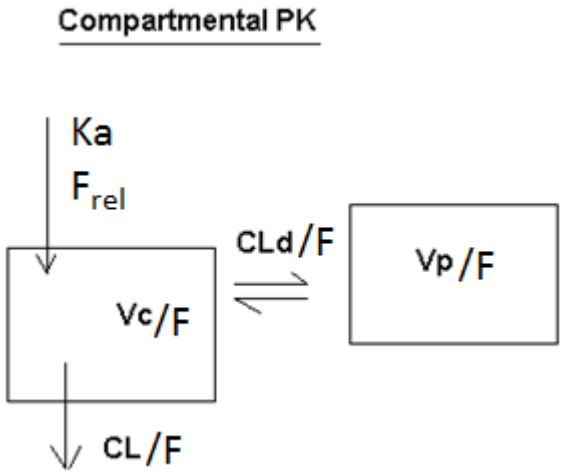
Summary "observed" PK vs. "Pop PK"

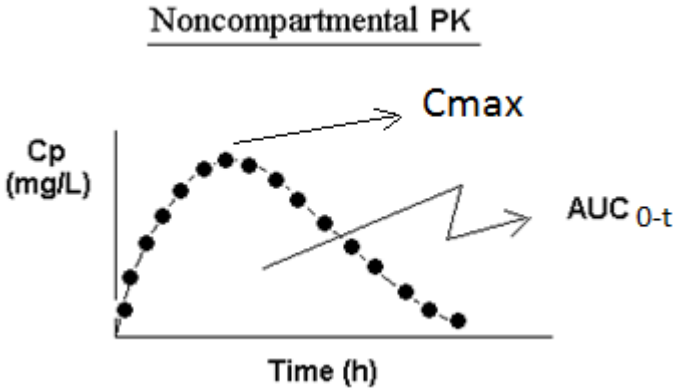
Population PK approach in PK Equivalence ("BE")

- For Biosimilars and other Products when distinguishing between "API" and "Formulation" differences is needed ?
- For Products with unstable or large baseline effect ?
- For nonlinear products ?
- For Topical products ?

Noncompartmental approach or "Observed" PK approach in PK Equivalence ("BE")

- For the rest, but always useful as a comparison method, as "fitted" results should be in agreement with "observed" ones





Population PK in BE

When it could be used: Iron Products

- Iron is and has been available commercially in many different forms:
  - Iron Dextran
  - Iron Gluconate
  - Iron Sucrose
- Iron is atypical in terms of its PK because:
  - Iron is NOT eliminated per se once it is in the systemic circulation.
  - Iron's distribution is non linear (from the RES to the Transferrin protein)
  - Once injected s/c, IM or IV, the "baseline" levels in terms of TBI and ferritin will change . In addition baseline changes also because of meals.

These three violates the assumptions needed for The noncompartmental approach to be robust

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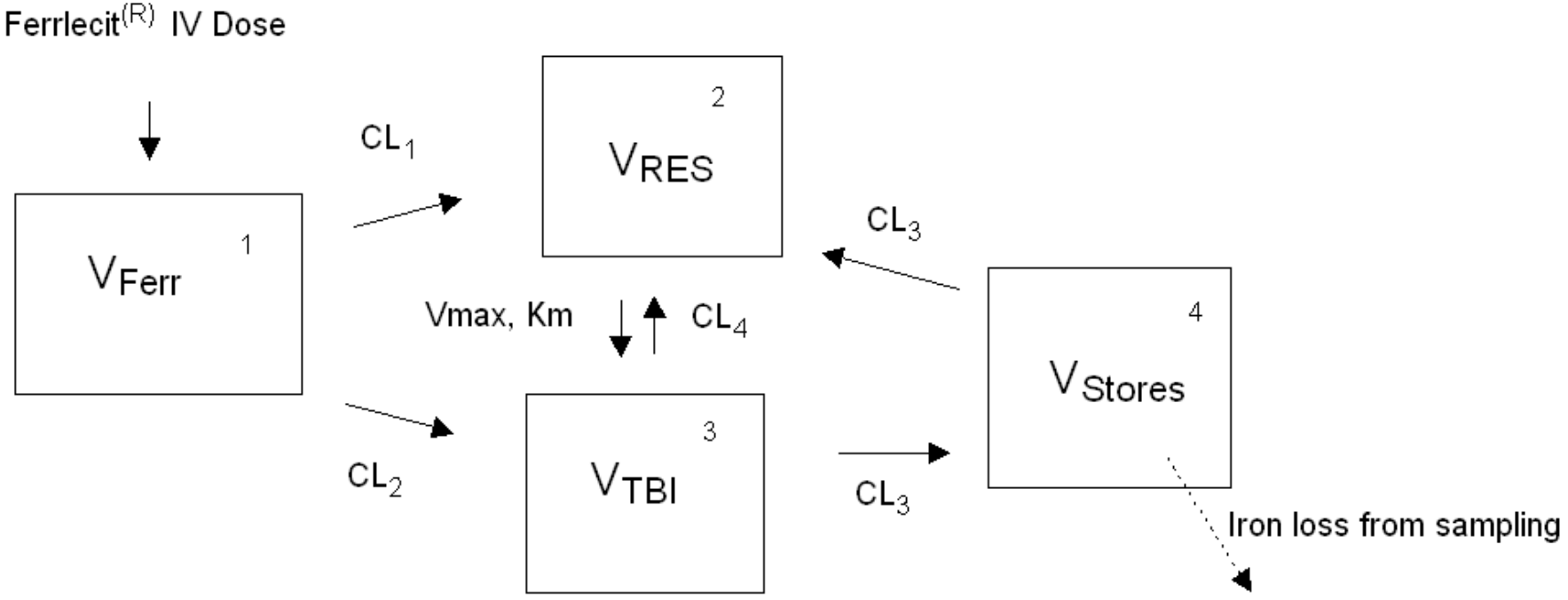
Published PK model of Iron Gluconate



Ref: Seligman PS, Dahl NV, Strobos J, Kimko HC, Schleicher R, Jones M, **Ducharme MP**. Single-dose pharmacokinetics of sodium ferric gluconate in sucrose complex in iron-deficient subjects. Pharmacotherapy 2004;24:574-583.

Ref.: Seng Yue C, Gallicano K, Labbe L, Ducharme MP. J Pharm Pharm Sci 2013;16(3):424-440.

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Population PK in BE

When it could be used: Iron Products

- "Old" OGD recommendations (prior to 2015) for Iron gluconate, iron sucrose and others:
  - Test/Reference Ratio and 90% CI for Cmax and AUC
    - Baseline adjusted Total serum iron
    - Baseline adjusted Transferrin-bound iron

But baseline changes constantly after dosing because iron is not eliminated except for the blood loss from Sampling plus the meals affect the baseline.

Ref.: Seng Yue C, Gallicano K, Labbe L, Ducharme MP. J Pharm Pharm Sci 2013;16(3):424-440.

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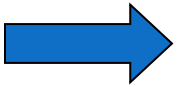
Population PK in BE

When it could be used: Iron Products

- Noncompartment approach (baseline adjusted Cmax and AUC for Total serum iron and TBI)
  - Is highly variable because baseline is not stable
  - Is not directly reflective of what is administered (i.e., Iron bound to either sucrose, gluconate or dextran)



With ABE necessitates an artificially large number of subjects (>100 in a 2 way crossover)

With SBE, then passing BE may be too easy as the baseline is not stable and this will artificially make it easier to pass

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Population PK in BE

When it could be used: Iron Products

- Using the proper PK model (as presented earlier and including the blood loss coming from the sampling), differences in Relative Bioavailability (Frel) can be demonstrated with a more reasonable number of subjects if the formulations are truly bioequivalent (e.g., <50 in a 2 way crossover with ABE)
- Assessment is also performed on iron administered (either bound to gluconate, sucrose or dextran) which is what is directly administered (eg, at baseline, the iron administered is ~ equal to Total serum iron – TBI)

Ref.: Seng Yue C, Gallicano K, Labbe L, Ducharme MP. J Pharm Pharm Sci 2013;16(3):424-440.

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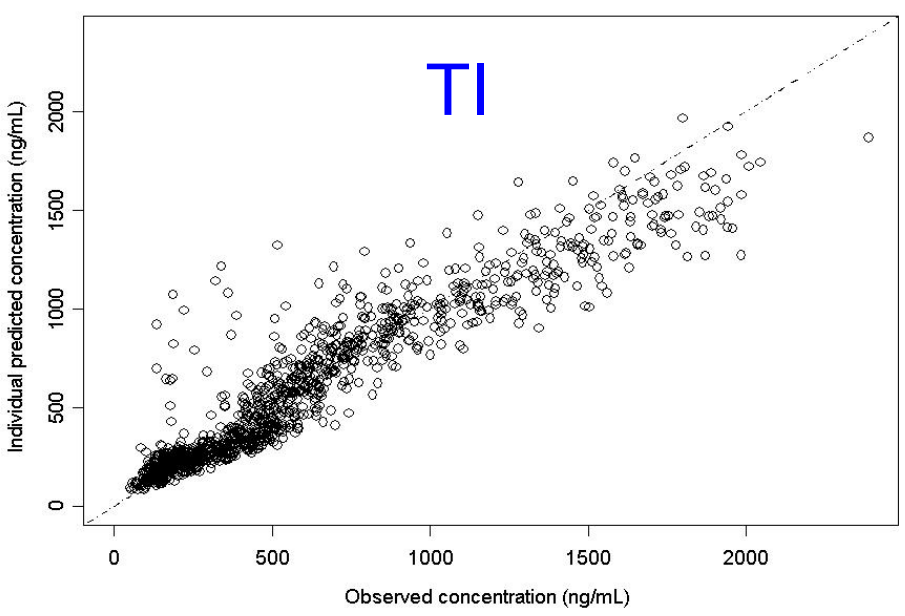
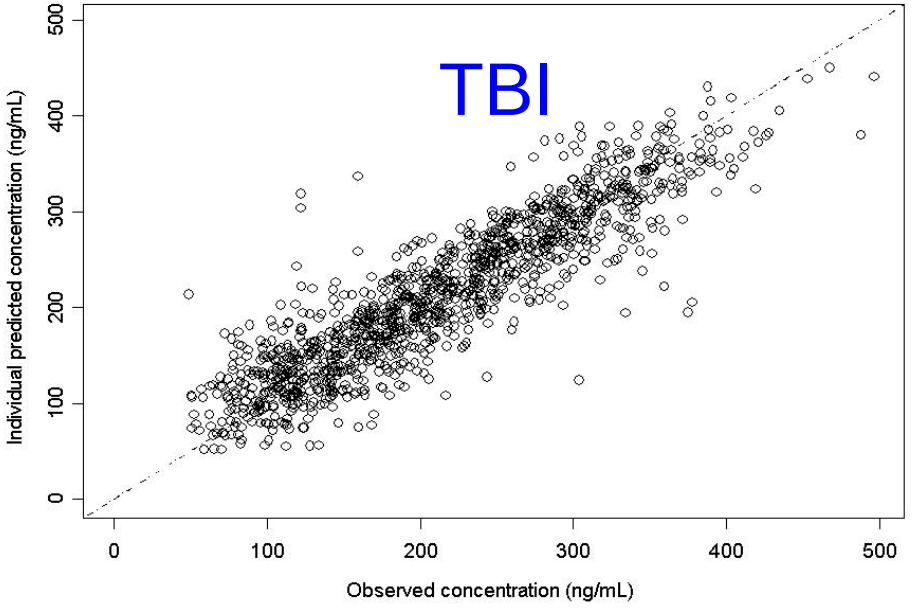
Population PK in BE

When it could be used: Iron Products





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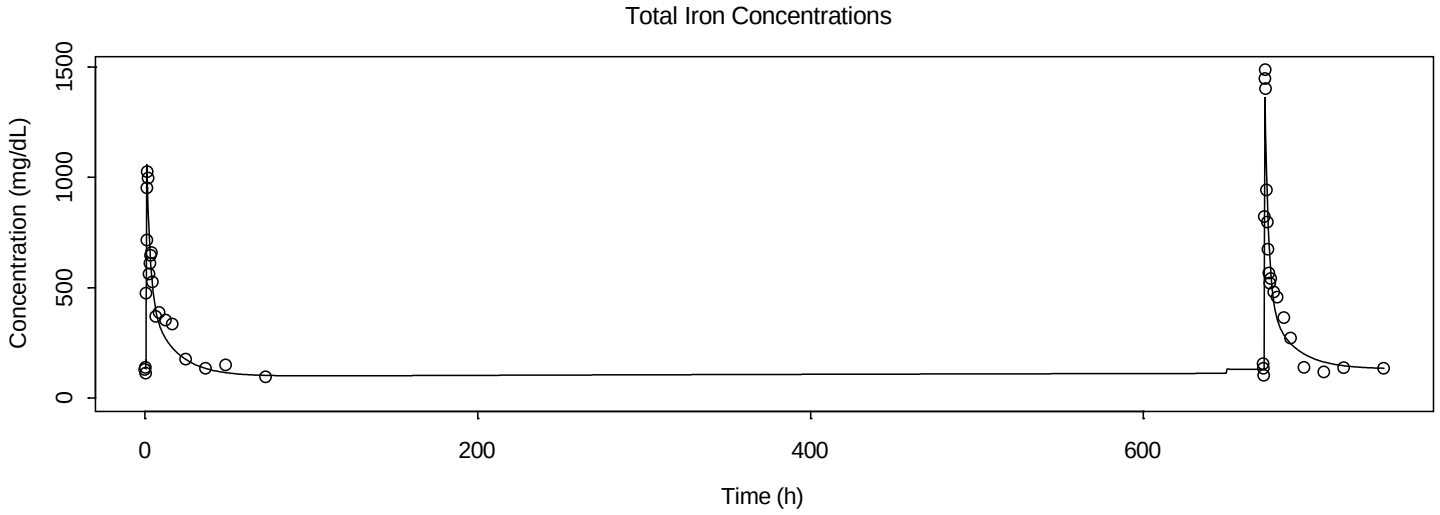

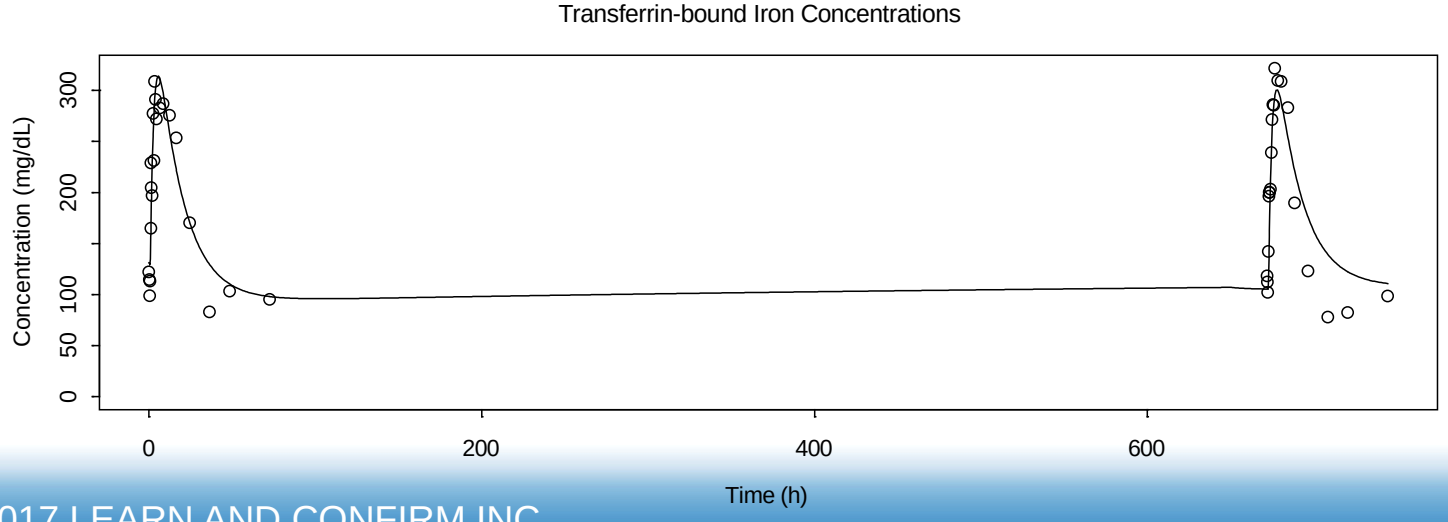

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Population PK in BE

When it could be used: Iron Products

Study	Analysis	Analyte	Cmax	AUC	Power
#1 (n=29)	CPT	Iron gluc.	89.9 (86 – 94)	89.7 (86 – 94)	>80%
	NCPT	TI	104.6 (86 – 127)	97.1 (74 – 127)	<40%
		TBI	95.9 (83 – 110)	119.7 (21 – 699)	
#2 (n=240)	NCPT	TI	100.4 (97 – 105)	99.7 (94 – 106)	>80%
		TBI	86.8 (83 – 91)	92.4 (86 – 100)	

Ref.: Seng Yue C, Gallicano K, Labbe L, Ducharme MP. J Pharm Pharm Sci 2013;16(3):424-440.

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Population PK in BE

When it could be used: Topical Products

Some Topicals contain APIs that are “locally’ acting in the skin and/or dermal regions and that are not intended for systemic action.

Preliminary data from a collaborative effort with Professor Isadore Kanfer of South Africa, an internationally recognized expert and research leader on Bioequivalence of Topical products.

Professor Kanfer has conducted a Tape Stripping Bioequivalence study on Reference (Zovirax®), Bioequivalent and Non-Bioequivalent cream formulations of Acyclovir.

My PhD student, Deniz Ozdin, presented preliminary results of a BE Population PK analysis of this data at last year’s AAPS annual meeting.

Ref.: Ozdin D, Reddy S, Patnala S, Kanfer I, Ducharme MP. Novel PK model using Tape Stripping data: Application in Bioequivalence assessment of two acyclovir topical cream formulations. Presented (Abstract #03R0830) at the 2016 AAPS Annual Meeting and Exposition, Denver, CO, USA, Nov 13-17 2016.

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Population PK in BE

When it could be used: Topical Products

Tape Stripping – a dermatopharmacokinetic approach

- U.S Food and Drug Administration (FDA). 1998. Guidance for Industry, Topical Dermatological Drug Product NDAs and ANDAs - *In Vivo* Bioavailability, Bioequivalence, *In Vitro* Release and Associated Studies
- Initial TS methodology outlining the bioavailability/bioequivalence protocol for topical formulations intended for local and/or regional activity, published in a draft guideline
- subject to criticism which resulted in its withdrawal, mainly due to a number of limitations, in particular the sources of variability and control

Ref.: Kanfer I. Strategies for the BE assessment of Topical dosage forms. AAPS BE, Biowaivers and Dissolution Conference, Dec. 7-8 2011.

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Population PK in BE

When it could be used: Topical Products

- Dermatopharmacokinetic approach
- Determines the amount of drug permeated into the *stratum corneum*
- Utilizes adhesive tape strips Transpore, Micropore, Scotch, D-Squame tapes
- Relatively non-invasive
- Removes layers of *stratum corneum*

Ref.: Kanfer I. Strategies for the BE assessment of Topical dosage forms. AAPS BE, Biowaivers and Dissolution Conference, Dec. 7-8 2011.

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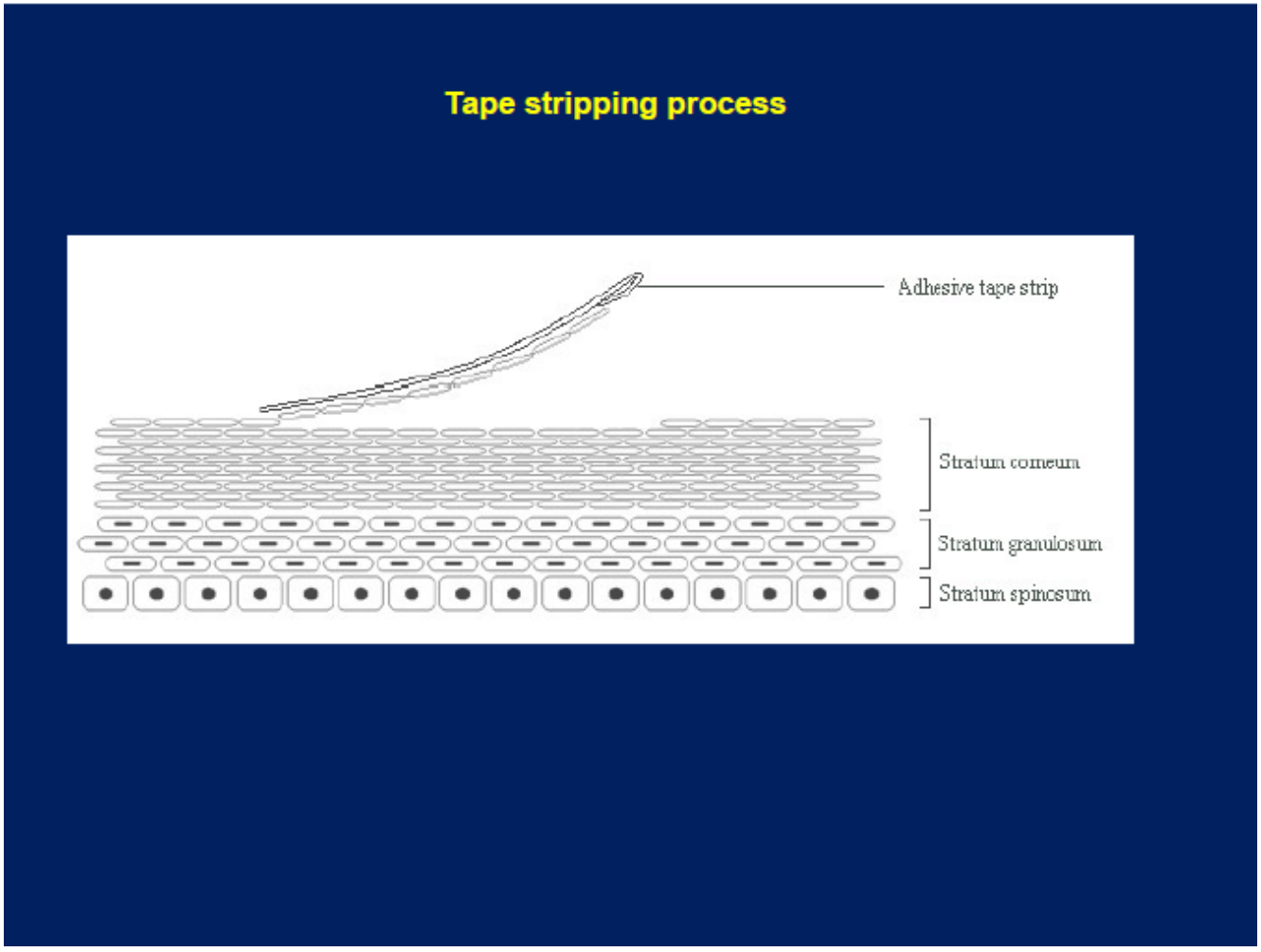
When it could be used: Topical Products



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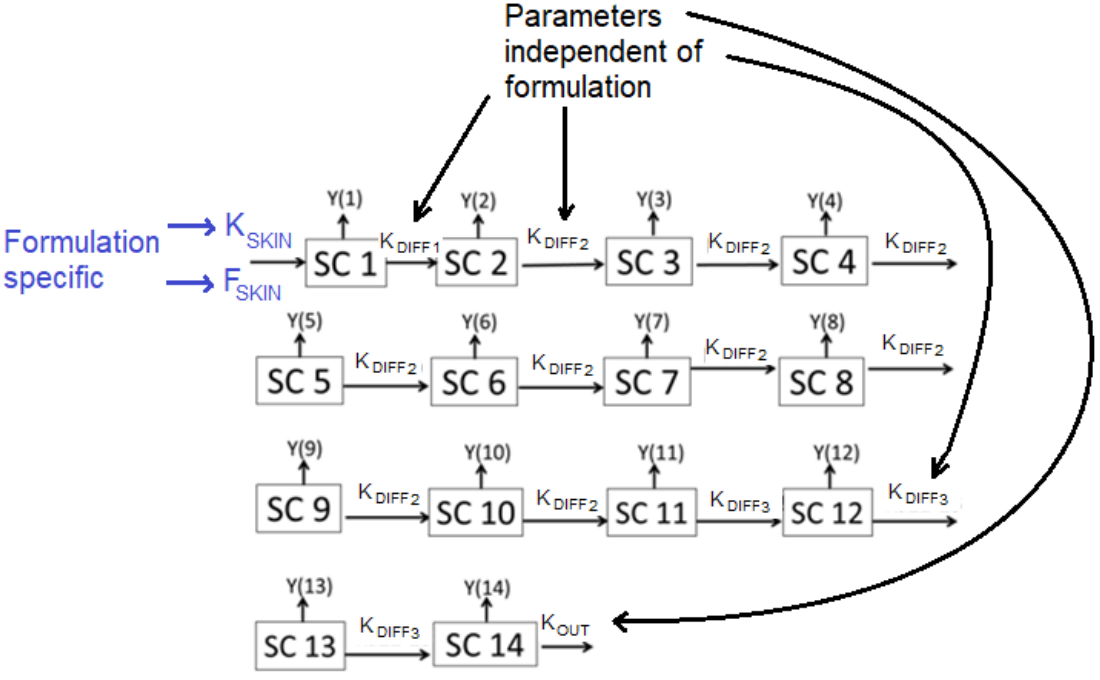
Population PK in BE

When it could be used: Topical Products

- A Population PK model was developed to fit and characterize the amounts of Acyclovir that was absorbed in the skin using the reference Zovirax® 5% cream, in a Tape Stripping study.

- The model was then used to fit the data generated by tape stripping for two different “generic” formulations of acyclovir cream: a BE 5% formulation (Adco®) and a non-BE 1.5% formulation (diluted).



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Population PK in BE

When it could be used: Topical Products

- Tape stripping study conducted in Healthy volunteers
- Crossover design, 2 studies:
  - Received Zovirax cream (n=20), a BE (n=20)
  - Received Zovirax cream (n=10), and a non-BE formulation (n=10)
- Cream applied at time 0
- Cream removed after 8 Minutes (established from the ED50)
- Tape stripping conducted on 14 different layers
- Amount of acyclovir present on the different layers measured by HPLC

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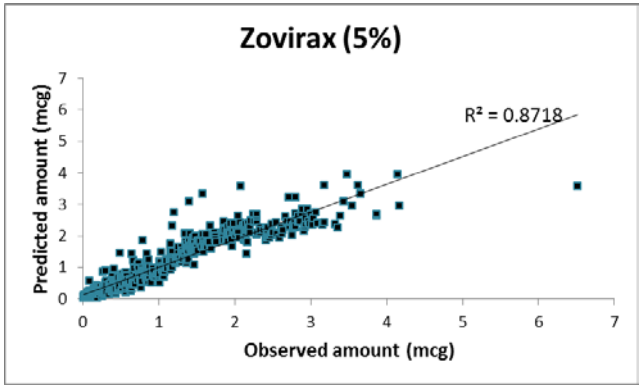
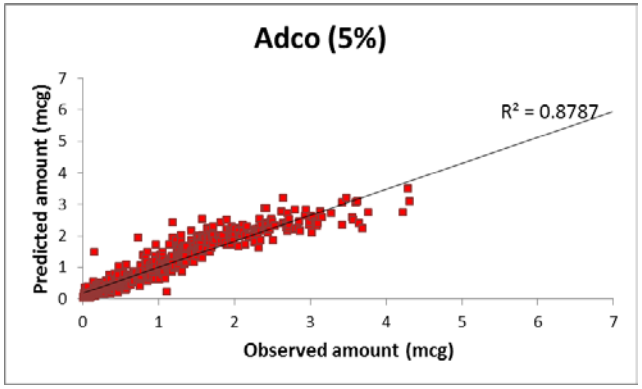
Population PK in BE

When it could be used: Topical Products





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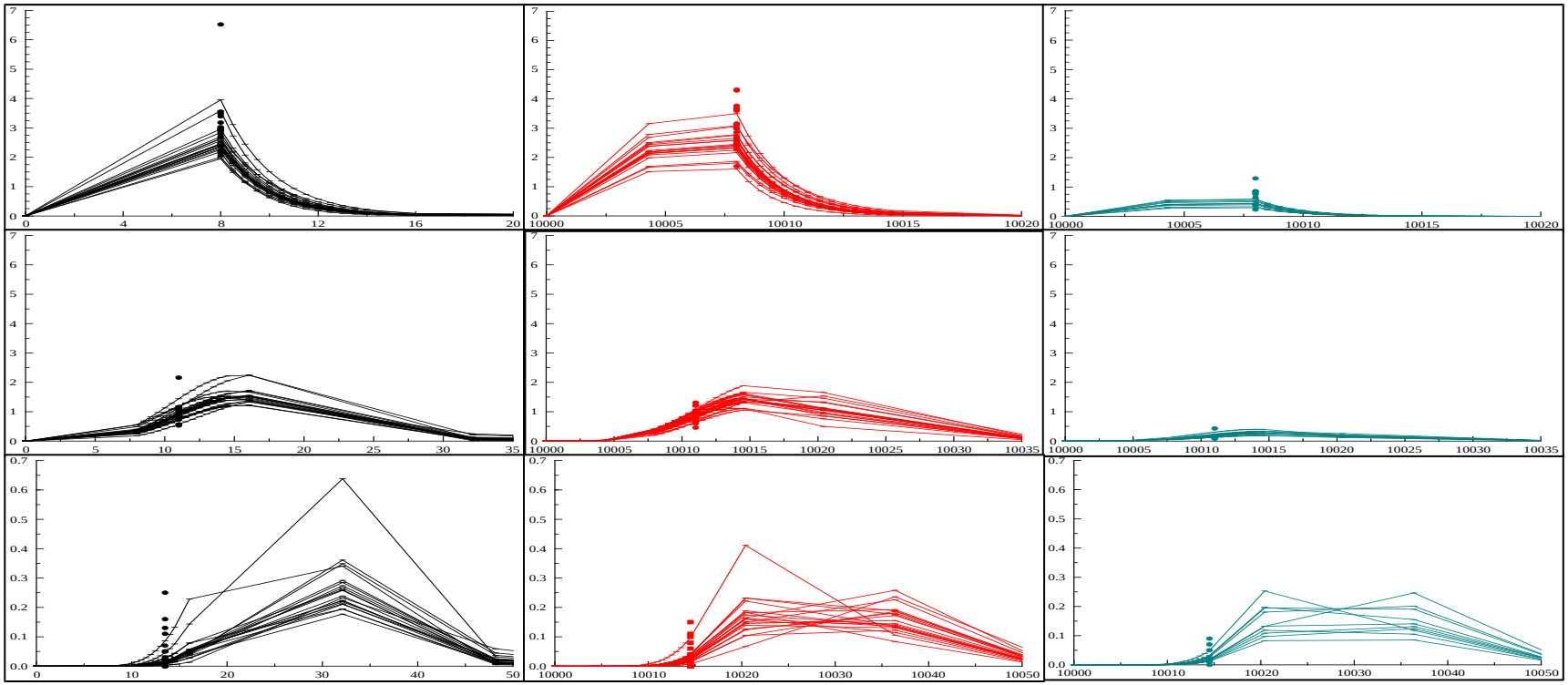
Population PK in BE

When it could be used: Topical Products

Acyclovir amount (mcg) in SC layers



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Population PK in BE

When it could be used: Topical Products

Estimated PK parameters of acyclovir RLD, BE and BIE formulations

Parameter	Geometric Mean (CV%)		
	RLD	BE	BIE
K_{SKIN} (min^{-1})	0.0016 (16.4%)	0.0016 (1.23%)	0.00044 (16.4%)
F_{SKIN} (absolute)	0.87 (16%)	0.85 (75%)	0.57 (17.2%)

Predicted results of relative bioequivalence between different acyclovir topical formulations versus the RLD

Parameter	BE		BIE	
	% Ratio of Geometric means	90% CI	% Ratio of Geometric means	90% CI
F_{SKIN}	94%	89%-99%	70%	65%- 75%
$K_{SKIN}(min^{-1})$	101%	95%-107%	38%	35%-41%

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Collaborators:

- Prof. Isadore Kanfer, Rhodes University & University of Toronto
- Dr. Philippe Colucci, Learn and Confirm Inc.
- Dr. Corinne Seng Yue, Learn and Confirm Inc.
- Deniz Ozdin, Bpharm, MSc, PhD Candidate, University of Montreal

Thank you!

Murray.Ducharme@learnandconfirm.ca