Novel approaches in human PK study design (e.g. stable isotopes technique) to overcome the challenges in the conduct of dedicated BA/BE studies-Case Studies

M-CERSI WORKSHOP
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Disclaimer & Acknowledgements

- Disclaimer:
  - I am a statistician
  - Last biology or chemistry class was in high school

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  - Manish Gupta
  - Alan Parr
  - Frank Hoke

Agenda

- Motivation
- Describe the Stable Isotope Label approach (SIL)
- Pilot Study
- Potential Benefits
- Limitations
- Summary

Motivation

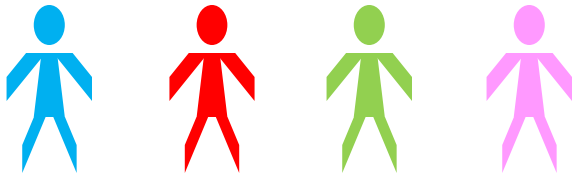
- Regulatory requirements for Quality by Design (QbD) of drug products
- Desire to link *in vitro* data (e.g. dissolution data) with *in vivo* data (e.g. human BA/BE studies)
- Traditional approaches to human BA/BE studies may not be feasible in many cases due required number of subjects

Re-introduce a Novel approach

Use of Stable Isotopes (SIL) in Pharmacokinetic Studies

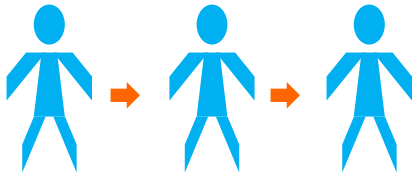
- Use of stable isotopes (has been in existence for many years.
- Provides the ability to measure plasma concentrations of an enriched and non-enriched drug substance from the same plasma sample (i.e., subject).
- The idea:
  - Dose two formulations at the same time in the same subject
  - Result in very small variability [Heck et al, 1979]

Parallel Grp: Between- or Inter-Subject Variability



IV

Crossover: Within- or Intra-Subject Variability

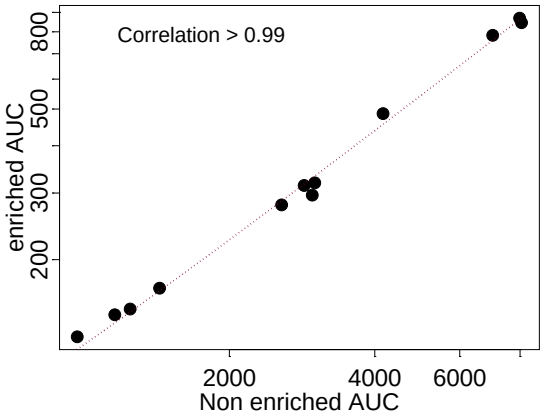


IV

SIL: Within- or Intra-Subject/period Variability

Stable Isotope Approach

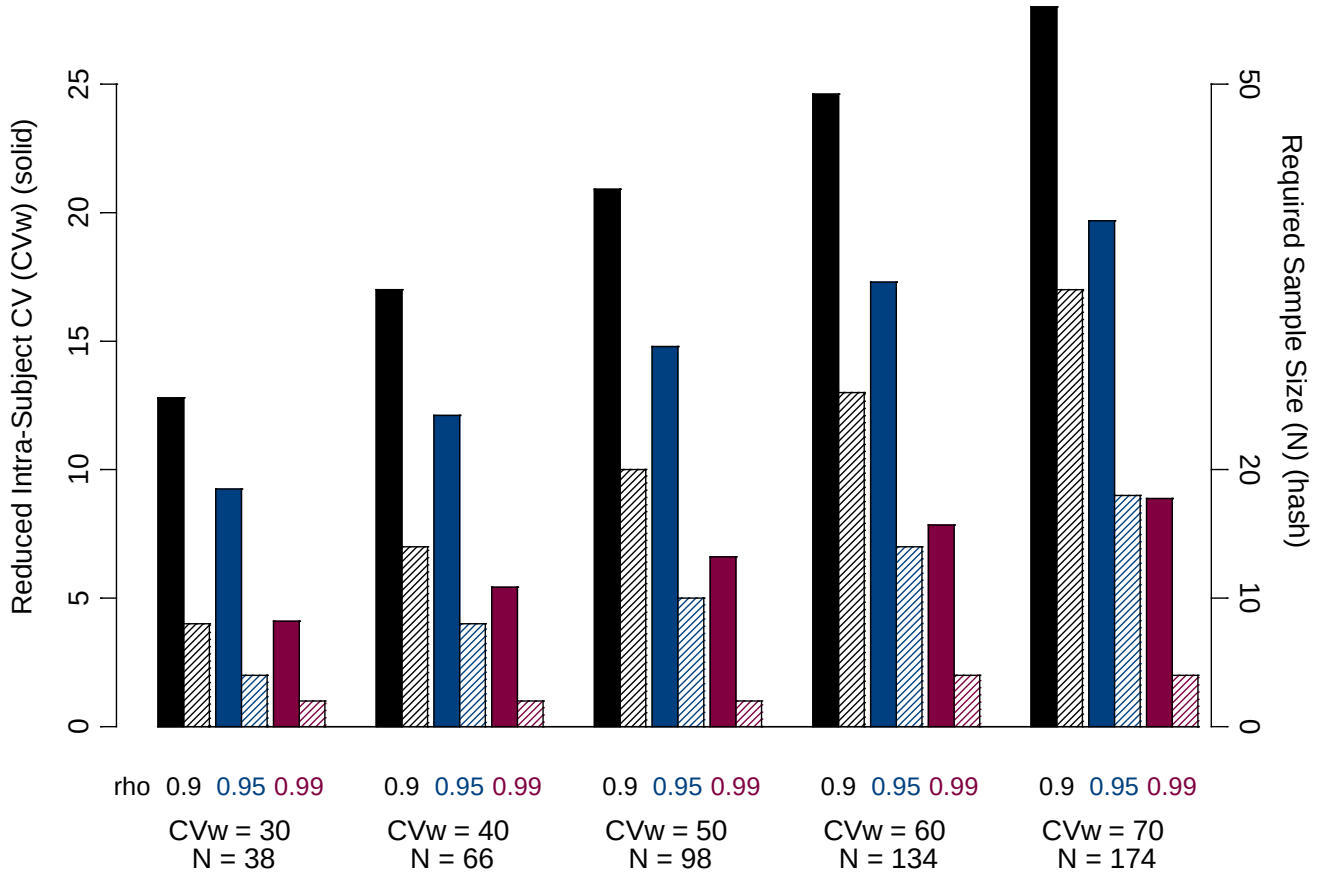
- Use the label drug (or SIL) as an internal control [Parr et al. 2012]
  - each subject at each dosing period will receive a small dose of the compound in question containing enriched isotope
- 2 PK parameters for each subject/dosing period (non-enriched and SIL)
  - Should be highly correlated (ρ > 0.95)
- Analysis “adjust” for the SIL resulting in the variability of the statistical test being reduced and subsequently reducing the required sample size



SIL – reduction in variability/sample size

Source Parr et al. 2012

Estimated intra-subject variability (solid bars) and required sample size (hashed bars)



For each combination of CV_w and rho, 1000 trials of 16 subjects were simulated and average residual mean square error (RMSE) was calculated. The PK parameters for both test and reference products and for the stable isotope was assumed to have a mean of 500, 500 and 50, respectively. The average RMSE presented as the reduced CV_w and the associated sample size required to provide 90% power to demonstrate bioequivalence are provided.

Caveat

- Methods **is only appropriate** under the assumptions that
  - Formulations that are qualitatively and quantitatively the same

  and
  - Subject/period are qualitatively and quantitatively the same

- What does this mean? May not be valid for
  - Formulations with different components
  - Drug interaction studies
  - Food effect studies
  - etc

Pilot Study

Objectives/Design

- Objectives
  - Known case of equivalence
  - Known case of in-equivalence
  - Known case of food effect

- 4 period crossover
  - Regimen A and B were the same oral formulation and dose
  - Regimen C same as oral formulation as A but 25% higher dose
  - Regimen D same as oral formulation as A but given with food
  - SIL – was an aqueous solution and 10% dose of A

- Planned sample size was 12 Normal Healthy Volunteers
  - Assume correlation of 0.95

- Analyzed both as a crossover and parallel group (using period 1 only, n = 3).

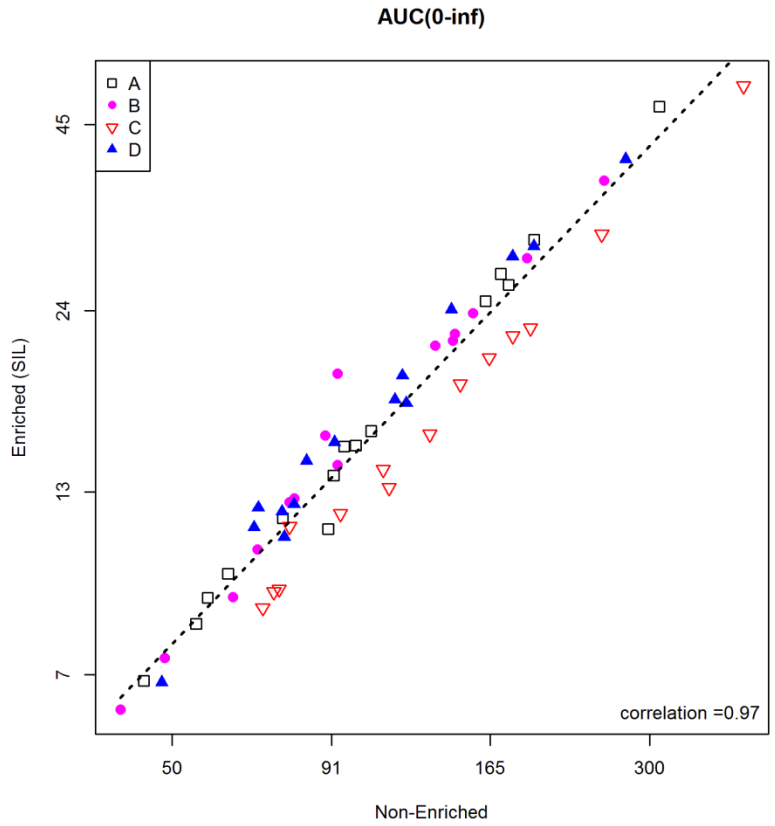
Pilot Study

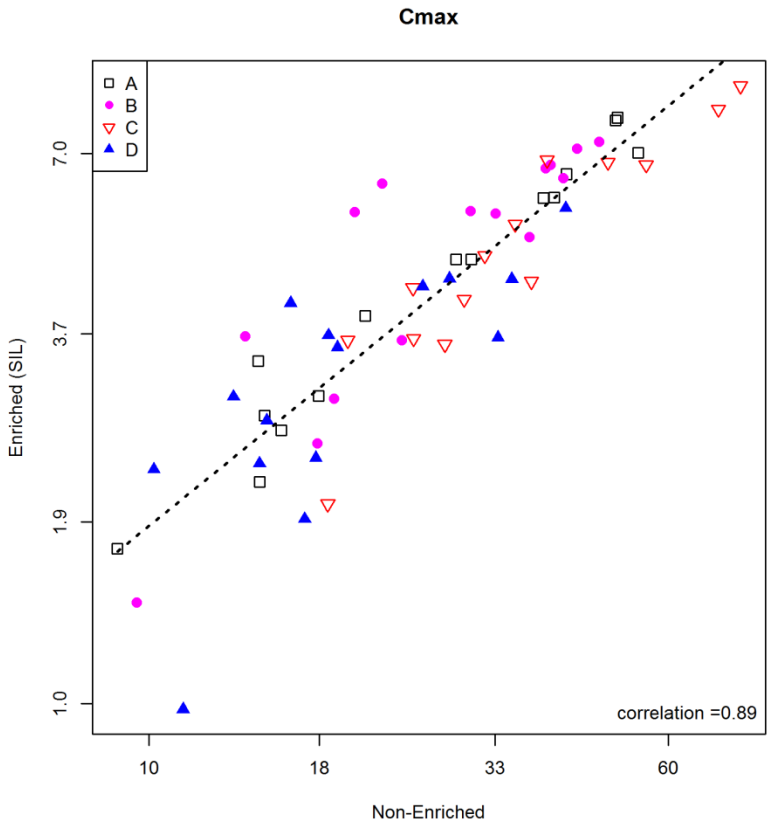
Results

- AUC correlation was as expected, but Cmax was lower (0.85-0.89).
- Cross-over
  - Large reduction in variability
  - Correct conclusions regarding BE, B:A was equivalent, C:A was in-equivalent.
  - Incorrect conclusions regarding food effect (D:A), a lack of effect was demonstrated for Cmax
- Parallel group
  - Large reduction in variability
  - Point estimates of ratios varied from expected values and thus resulted in failure to draw correct inference in some cases.
  - Similar results when data from periods 2, 3 & 4 were analyzed

Pilot Study

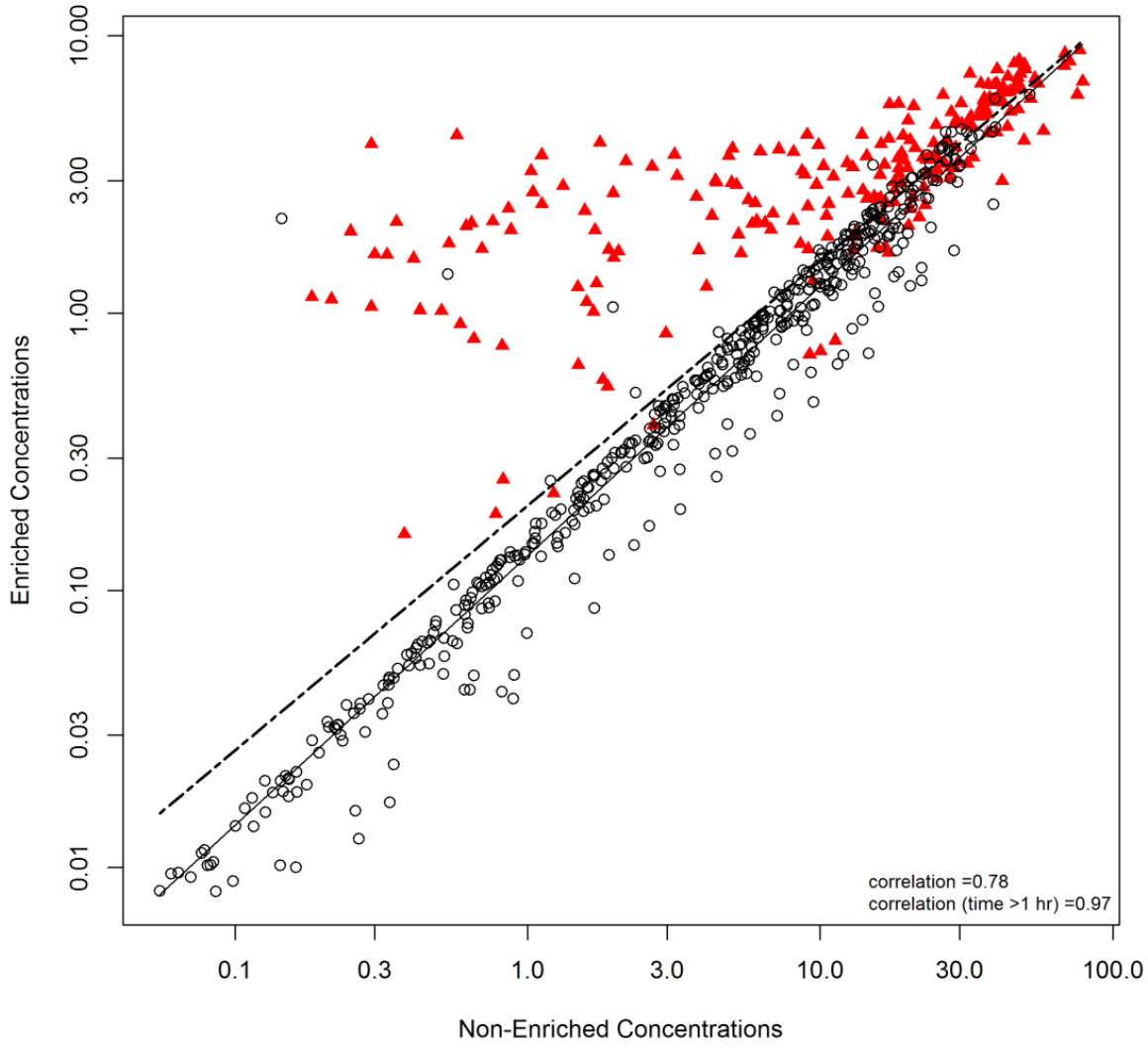
Lower than expected correlation in Cmax

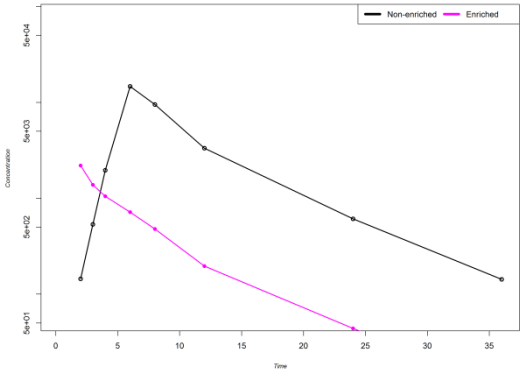




Pilot Study

Lower than expected correlation in Cmax





- Red Triangles: PK samples collected prior to 1 hr post dosing

Pilot Study

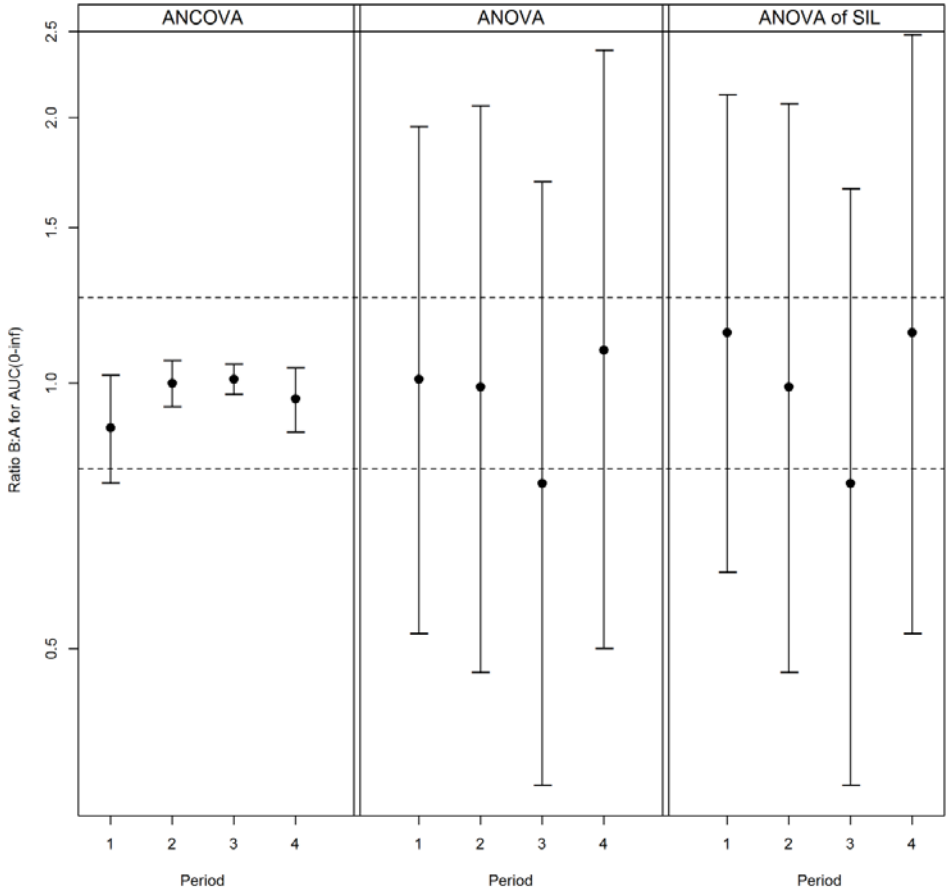
Incorrect inference in Food Effect

Parameter	Geometric Lsmean Test Tmt.	Geometric LSmean Ref. Tmt.	Ratio	90% Confidence Interval	CVw%
Cmax(units)	25892.1	25253.2	1.03	(0.89,1.18)	21.83
Cmax(units)	19484.4	25907.3	0.75	(0.61,0.92)	33.55
Cmax(units)	3087.9	4259.8	0.72	(0.63,0.84)	23.90

- Food decreased the absorption of both non-enriched and SIL formulations
- Adjusting for the SIL in the model, masks the food effect
- Ratio of 0.75 / 0.72 = 1.04

Pilot Study

Inconsistent results in parallel group



Stable Isotope Advantages

Advantages

a. Enriched isotope acts as reference within each subject/period reducing variability
b. Decreases number of subjects required to achieve desired power
c. Reduces number of dosing periods (when compared to the current replicate design approach for highly variable drugs)
d. Reduces overall cost of PK studies
e. Does not require the manufacture of large amounts of enriched drug substance
f. Does not require the manufacture of formulations containing the enriched isotope
g. Reduces number of PK samples that need to be analyzed
h. Doesn’t use radioactivity

Stable Isotope Limitations

Limitations

a. Need to confirm that there is no isotope effect (usually not seen if we don't use deuterium)
   - Satisfy the "qualitatively and quantitatively the same" assumption

b. Need to have enriched isotope compound synthesized to do these studies (estimated cost is 10K pounds & 12 weeks)

c. May need to synthesize two different enriched isotopes if one is needed as an internal standard for analytical analysis purposes (not an issue since multiple compounds can be made)

d. Time and cost to synthesize these compounds so that the labelled site is metabolically stable (this can be built into the project plans)

When would you use this approach?

- For compounds that exhibit high PK variability
- For compounds where subject/ patient recruitment is difficult
- Comparison of products manufactured at different sites
- Formulation/ Process screening studies
- Animal studies where small number of animals are used
- Many others

Note: Stable isotope approach adds value even if compound exhibits acceptable bioavailability

References

Heck HA, Buttrill SE, Flynn NW, Dyer RL, Anbar M, Cairns T, Dighe S, Cabana BE. (1979). Bioavailability of imipramine tablets relative to a stable isotope-labelled internal standard: increasing the power of bioavailability tests. J Pharmacokinet Biopharm. 1979;7(3):233–48.

Parr A, Gupta M, Montague TH and Hoke F (2012). Re-introduction of a Novel Approach to the Use of Stable Isotopes in Pharmacokinetic Studies. The AAPS Journal (2012), DOI: 10.1208/s12248-012-9371-4