Model-informed Drug Development for Dose Confirmation in Special Populations

Full Covariate Modeling meets Intersection-Union Testing

Jim Rogers, Ph.D.

International Symposium on Biopharmaceutical Statistics
March 6-9, 2024, Baltimore, MD

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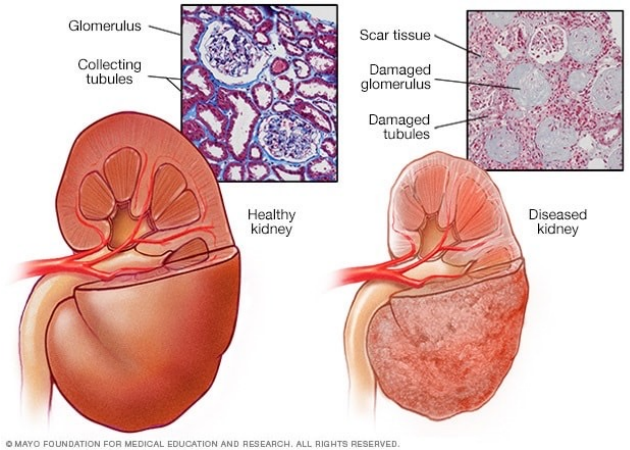
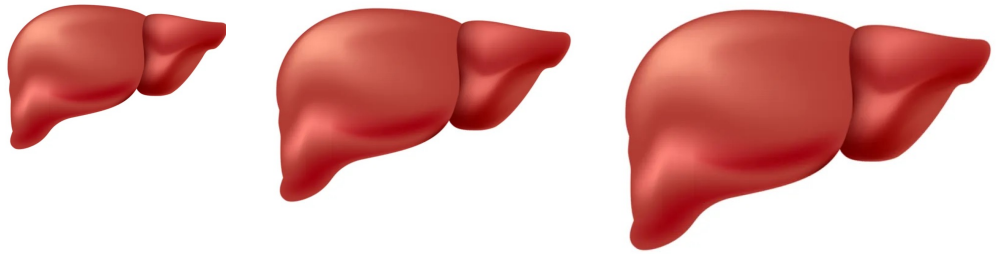
~~The Right Dose~~ The Right Dose *For You*

Same dose regardless of kidney health?



Same dose regardless of liver size?



Same dose regardless of age?

Population Pharmacokinetics

Guidance for Industry

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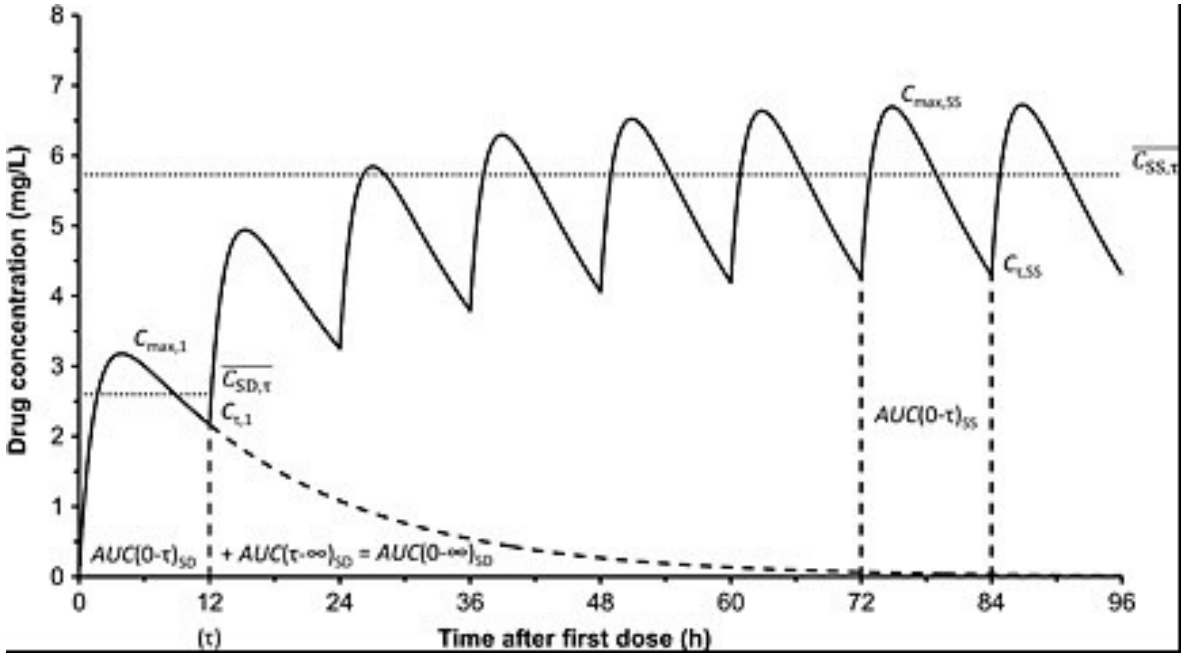
My Goals for This Talk

1. There are well-established practices for much of what I'm going to describe.
2. The "best version" of the status quo is fine, *as far is it goes*.
3. My goals are:
   - To clarify what the "best version" status quo does and doesn't achieve
   - To suggest where further work is most needed

Pharmacokinetic (PK) Covariate Modeling



BIOPHARMACEUTICS & DRUG DISPOSITION
Biopharm. Drug Dispos. **36**: 93–103 (2015)
Published online 21 January 2015 in Wiley Online Library
(wileyonlinelibrary.com) **DOI**: 10.1002/bdd.1923

Proposal for defining the relevance of drug accumulation derived from single dose study data for modified release dosage forms

Christian Scheerans*, Roland Heinig, and Wolfgang Mueck
Clinical Pharmacology, Bayer Pharma AG, Research Center, Wuppertal, Germany

In simple cases:

$$AUC_i = \frac{F \cdot Dose}{\exp\left(\theta_0 + \sum_{l=1}^{L} \theta_l \log\left(\frac{X_{il}}{X_l^{(\mathrm{ref})}}\right) + \eta_i\right)}$$

Parameters on the right-hand side can be estimated from a NLME

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Fixed Effect Forest Plots

Simultaneous population pharmacokinetic analysis of total and unbound valemetostat in patients with non-Hodgkin lymphoma to quantify the effect of the binding protein, alpha 1-acid glycoprotein

Masato Fukae (1), Kyle Baron (2), Masaya Tachibana (1), John Mondick (2), Takako Shimizu (1)
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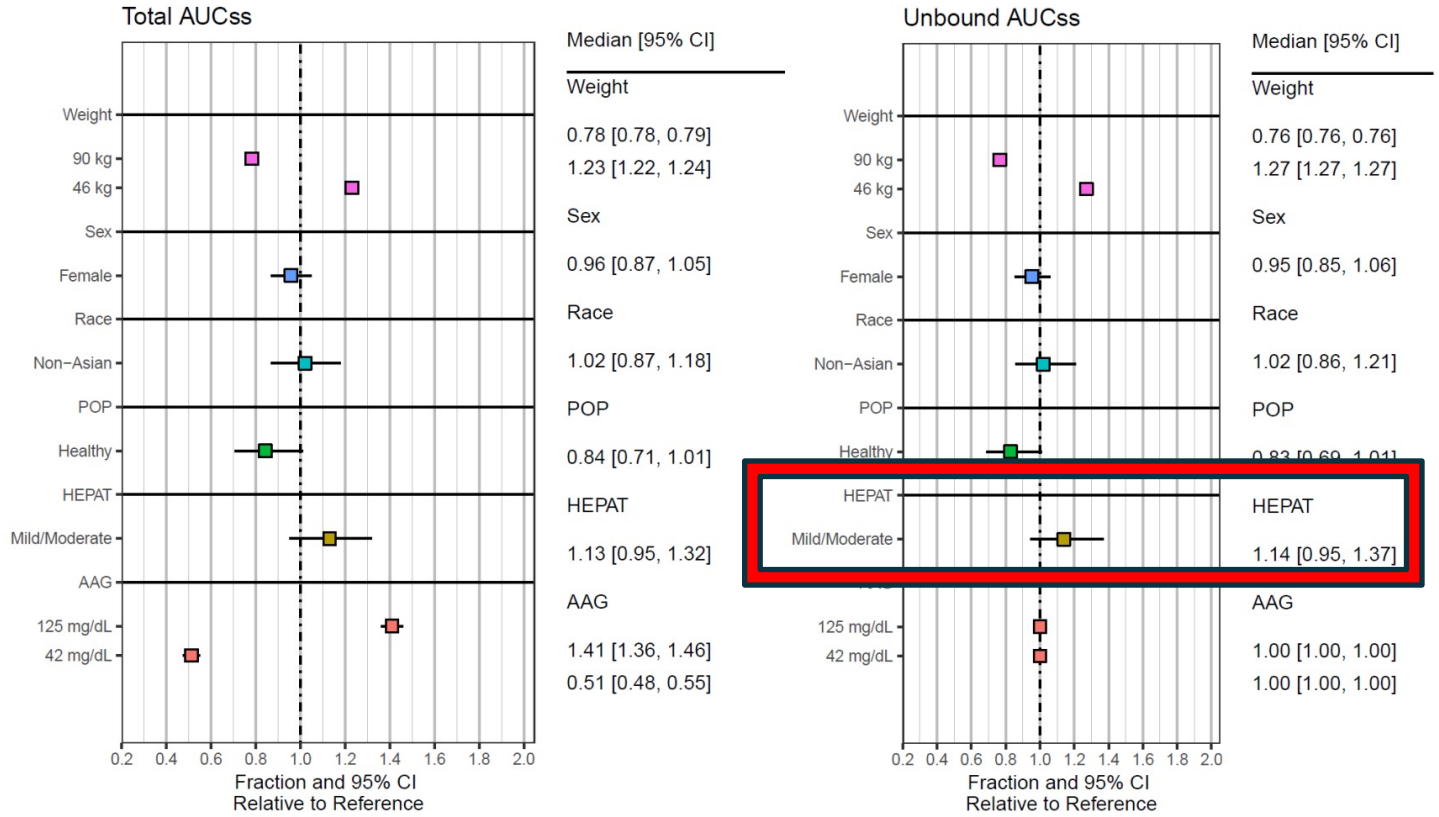
Fig. 5 The effect of each covariate in the final model on the total and unbound AUCss



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1. *Simulations Based on Fixed-Effect Estimates*
2. *Simulations Based on Uncertainty of Fixed-Effect Estimates*

Fixed effect CIs alone may or may not be sufficient to support dose adjustment decisions (more on this later). Sometimes we also need:

3. *Simulations Based on Estimates of Between-Subject Variability*

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Connecting CIs with Confirmatory Decisions

Initial progress towards a confirmatory decision framework:

British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2018) **84** 1525–1534 1525

ORIGINAL ARTICLE

Full covariate modelling approach in population pharmacokinetics: understanding the underlying hypothesis tests and implications of multiplicity

Correspondence Xu Steven Xu, Janssen Research & Development, LLC, 920 Route 202, Raritan, NJ 08869, USA. Tel.: +1 908 927 4979; Fax: +1 908 203 1527; E-mail: sxu26@its.jnj.com

Received 20 October 2017; **Revised** 5 February 2018; **Accepted** 2 March 2018

Xu Steven Xu[1,*], Min Yuan[2,*], Hao Zhu[3], Yaning Yang[4], Hui Wang[5], Honghui Zhou[1], Jinfeng Xu[6], Liping Zhang[1] and Jose Pinheiro[1]

Summary of framework

- ✓ Start from a "full covariate model" framework (we need a confidence interval for each effect of interest).
- ✓ Establish formal connection between CIs and decision making
- ❑ Control family-wise error rate (FWER) when testing for clinically meaningful differences

$$H_{0j} : |\beta_j| \leq \Delta; H_{1j} : |\beta_j| > \Delta$$

I like the spirit of this paper, but I am going to argue for a re-formulation that controls a different FWER

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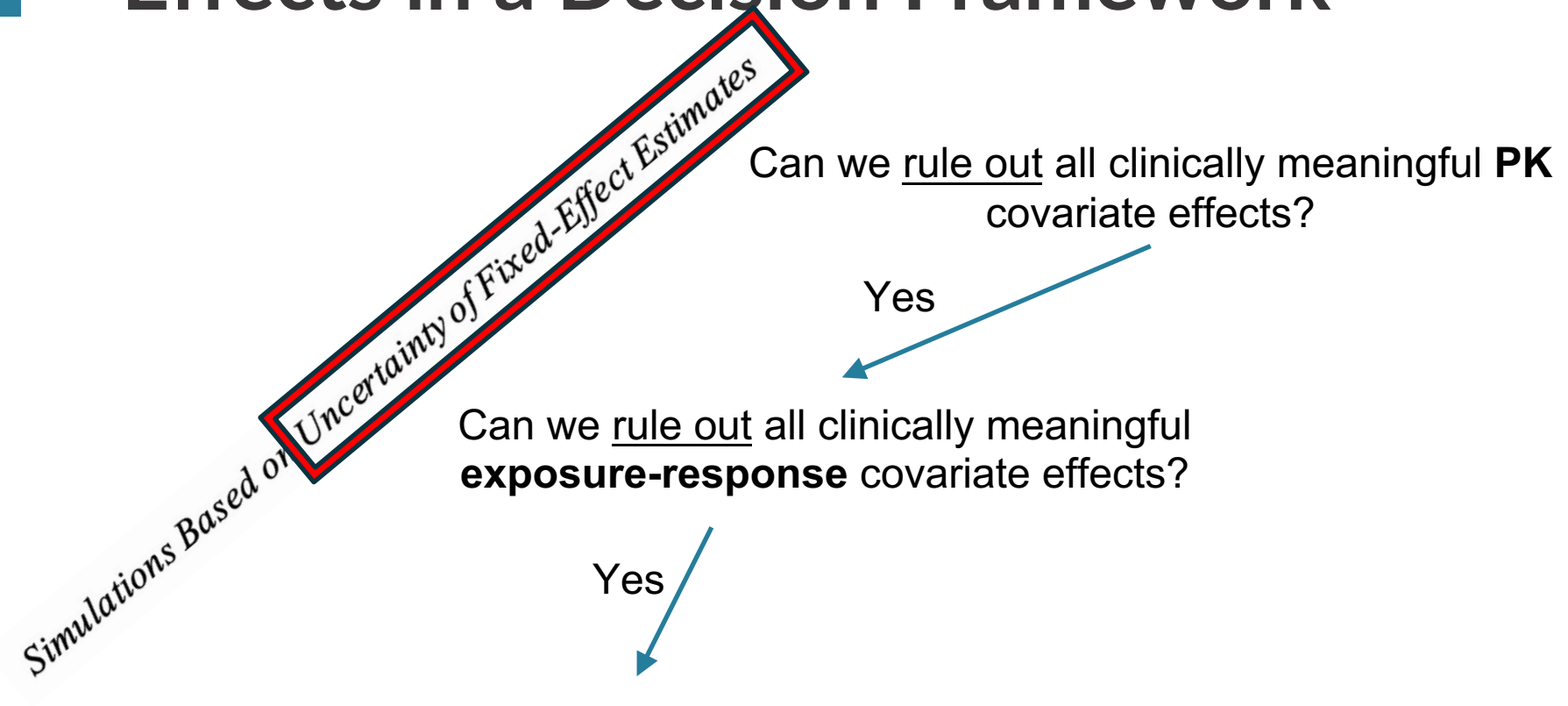
Embedding Confidence Intervals for Covariate Effects in a Decision Framework



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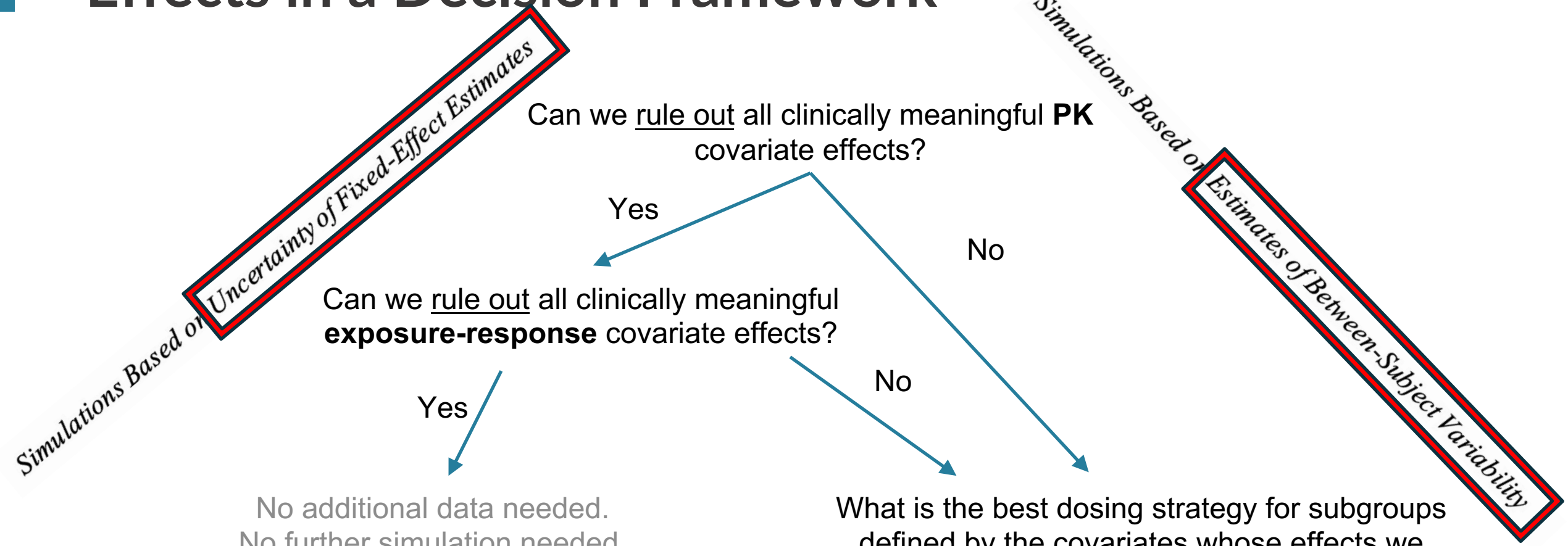

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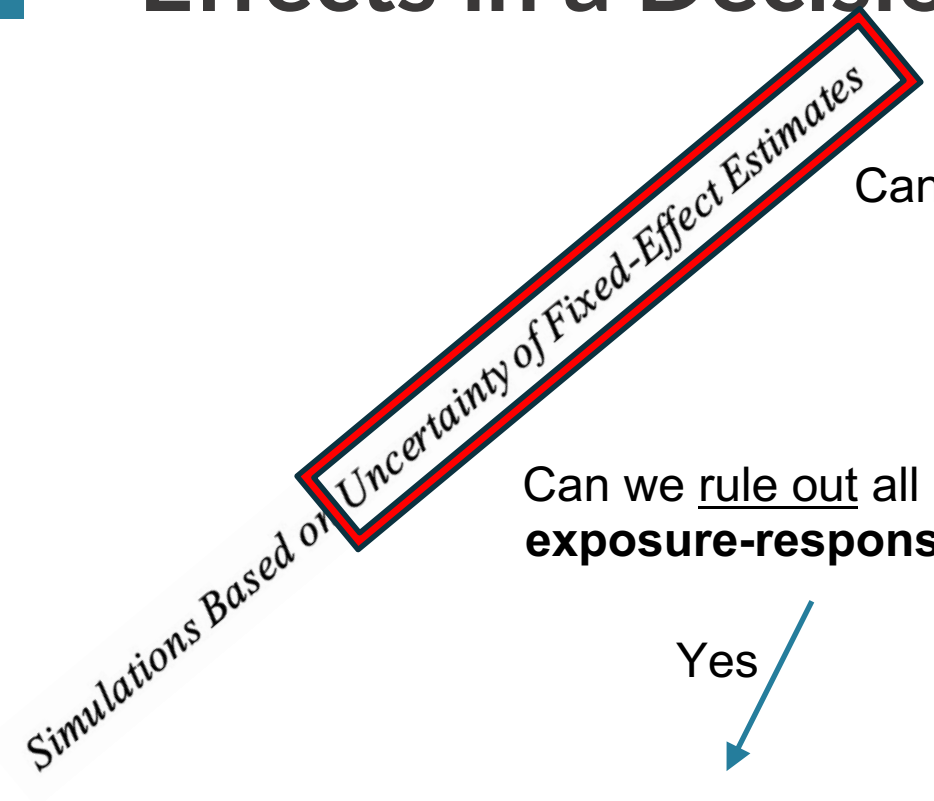

Can we rule out all clinically meaningful **PK** covariate effects?

Yes

Can we rule out all clinically meaningful **exposure-response** covariate effects?

Yes

No additional data needed.
No further simulation needed.
No dosing adjustments needed.

Along this path we need:

- **Evidence of absence, not just absence of evidence**
- **Confidence intervals ("full covariate modeling"),**
- **Practical equivalence framework ("intersection-union testing").**

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Practical Equivalence Hypothesis Testing to "Rule Out" Clinically Meaningful Effects

Statistical Science
1996, Vol. 11, No. 4, 283–319

Bioequivalence Trials, Intersection–Union Tests and Equivalence Confidence Sets

Roger L. Berger and Jason C. Hsu

$$H_0: \quad \frac{\mu_T}{\mu_R} \le \delta_L \quad \text{or} \quad \frac{\mu_T}{\mu_R} \ge \delta_U \tag{1}$$

versus

$$H_a: \quad \delta_L < \frac{\mu_T}{\mu_R} < \delta_U.$$

$$H_0: \theta \in \bigcup_{i=1}^{k} \Theta_i \quad \text{versus} \quad H_a: \theta \in \bigcap_{i=1}^{k} \Theta_i^c, \tag{9}$$

THEOREM 1. *If R_i is a level-α test of H_{0i}, for $i = 1, \ldots, k$, then the intersection–union test with rejection region $R = \bigcap_{i=1}^{k} R_i$ is a level-α test of H_0 versus H_a in (9).*

5. CONFIDENCE SETS AND BIOEQUIVALENCE TESTS

5.1 A 100(1 − α)% Confidence Interval

We will show that the $100(1-\alpha)\%$ confidence interval $[D_1^-, D_1^+]$ given by

$$\left[\left(D - t_{\alpha,r}\mathrm{SE}(D)\right)^-, \left(D + t_{\alpha,r}\mathrm{SE}(D)\right)^+\right] \tag{16}$$

corresponds to the size-α TOST for (2). Here $x^- = \min\{0, x\}$ and $x^+ = \max\{0, x\}$. The $100(1-\alpha)\%$ interval (16) is equal to the $100(1-2\alpha)\%$ interval (8) when the interval (8) contains zero. But, when the interval (8) lies to the right (left) of zero, the interval (16) extends from zero to the upper (lower) endpoint of interval (8).

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Building on Prior Recommendations

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My proposed modification:

- ✓ Start from a “full covariate model” framework (we need a confidence interval for the effect of interest).
- ✓ Establish formal connection between CIs and decision making
- ✓ Control family-wise error rate (FWER) ~~when testing for clinically meaningful differences~~ when testing for practical equivalence

$$H_{0j} : |\beta_j| \leq \Delta ; H_{1j} : |\beta_j| > \Delta$$

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Evidence to Justify “No Dose Adjustment”

Is there sufficient evidence that:

Hepatic impairment doesn’t make your exposure too high
AND
Hepatic impairment doesn’t make your exposure too low
AND
Renal impairment doesn’t make your exposure too high
AND
Renal impairment doesn’t make your exposure too low
AND
Concomitant medications don’t make your exposure too high
AND
Concomitant medications don’t make your exposure too low
… et cetera …

To evaluate evidence for a proposition in a hypothesis testing framework, the proposition needs to be formalized as the **alternative** hypotheses

This global alternative hypothesis corresponds to an **intersection** of individual alternative hypotheses

We can therefore apply union-intersection testing principles and test each of these hypotheses **without multiplicity adjustment**, while still controlling the relevant FWER

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Practical Implementation

1. Construct fixed effect CIs “the same way we always have”.
2. Do *not* increase the width of the CIs. If anything, *reduce* the nominal per-interval width from 95% to 90% (to achieve global FWER control < 5%).
3. If **all** intervals lie **entirely** within the [0.8, 1.25] practical equivalence region, interpret this as evidence that no dose adjustment is necessary.
4. Otherwise, do population simulations with between-subject variation in subgroups defined by the covariates whose effects have not been ruled out

Fixed Effect Forest Plots

Simultaneous population pharmacokinetic analysis of total and unbound valemetostat in patients with non-Hodgkin lymphoma to quantify the effect of the binding protein, alpha 1-acid glycoprotein

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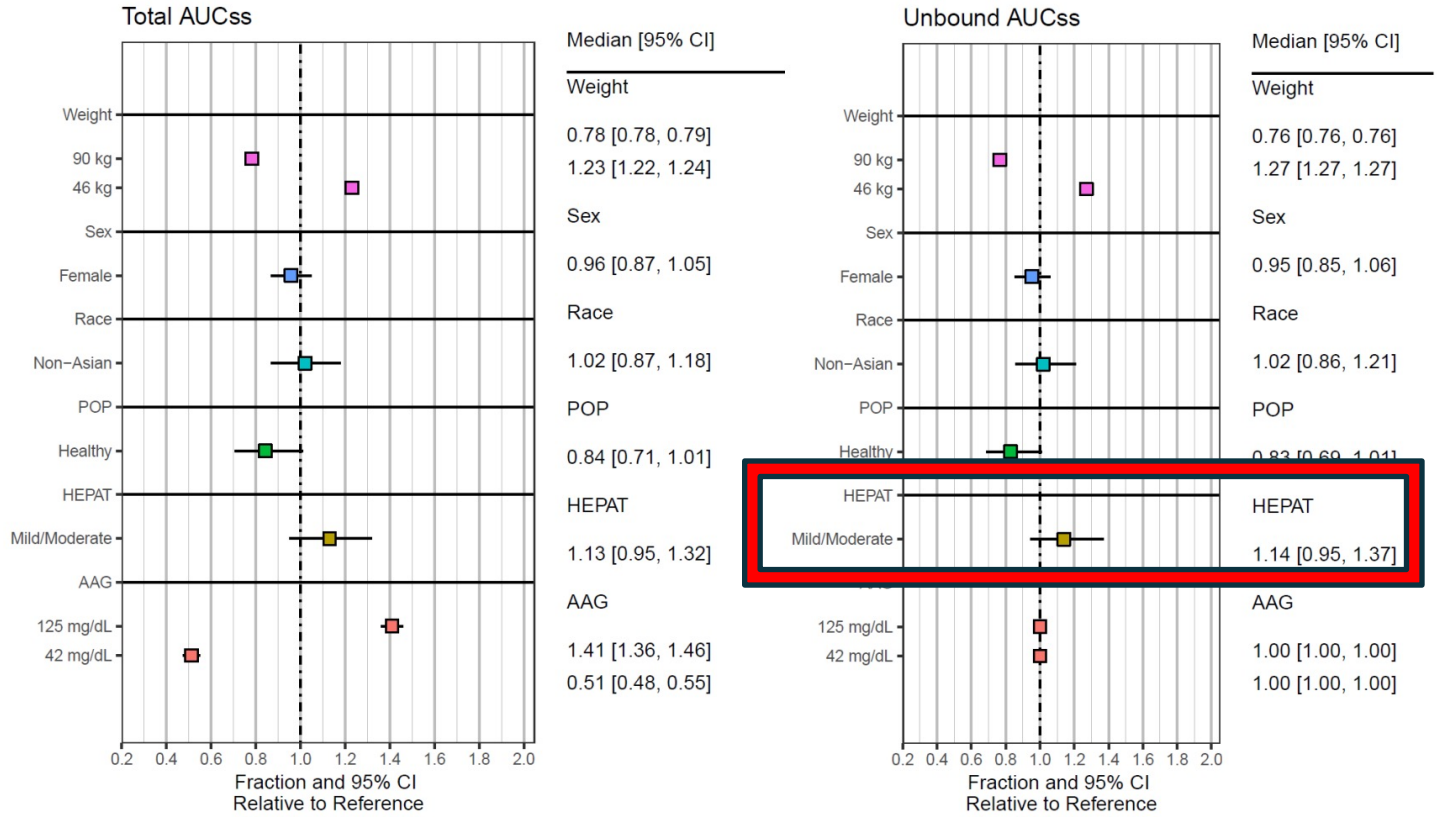

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Fixed effect CIs alone may or may not be sufficient to support dose adjustment decisions (more on this later). Hence the need for:

3. *Simulations Based on Estimates of Between-Subject Variability*

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Simulations Based on Estimates of Between-Subject Variability

Landmark and longitudinal exposure-response analyses for multiple efficacy and safety endpoints to justify the clinical dose of valemetostat for adult T-cell leukemia/lymphoma

Masato Fukae (1), Kyle Baron (2), James Rogers (2), Ramon Garcia (2), Masaya Tachibana (1), John Mondick (2), Takako Shimizu (1)
(1) Daiichi Sankyo Co., Ltd. Tokyo, Japan, (2) Metrum Research Group, Tariffville, CT, USA

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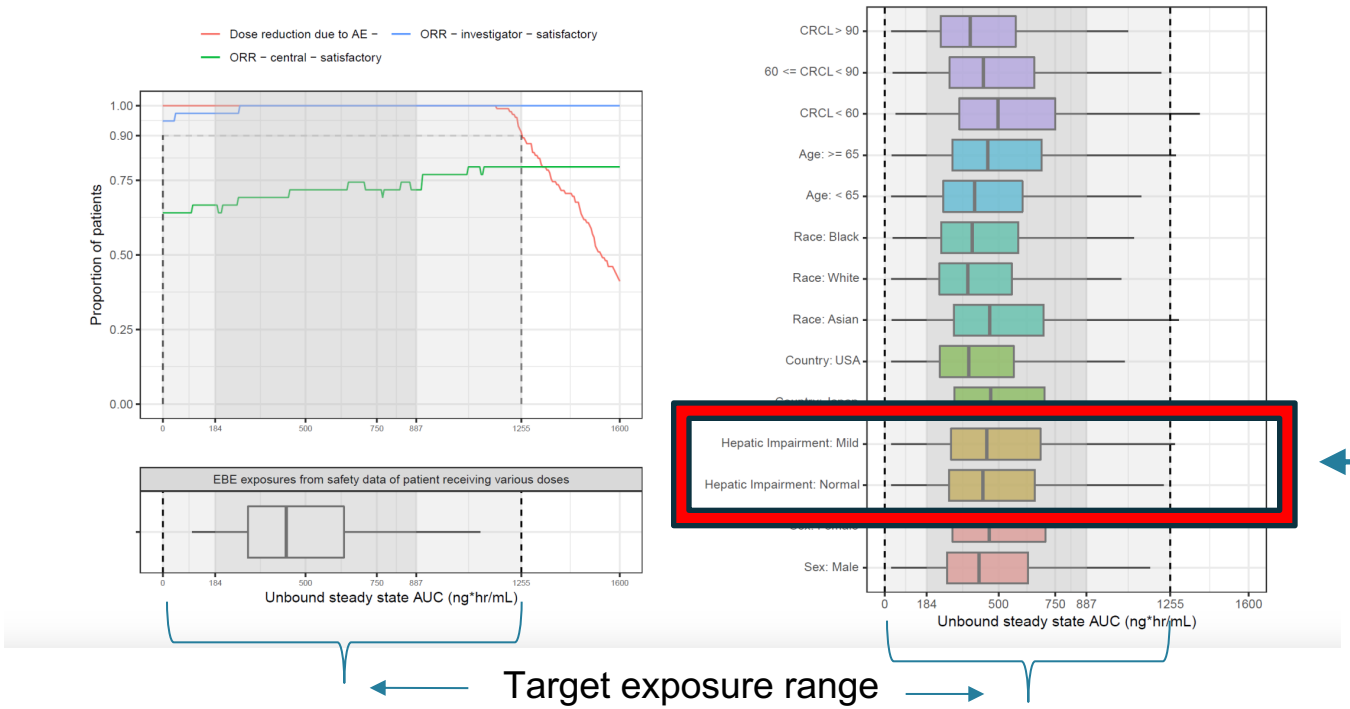
3. *Simulations Based on Estimates of Between-Subject Variability*

Fig. 3 Estimated ROPE based on the definition (**left**) and expected exposure range of sub-population administered 200 mg QD (**right**). The light and dark gray areas indicate the ROPE and modified ROPE, respectively.



Target exposure range
defined by exposure-response

Notwithstanding moderate effect of hepatic impairment, the standard dose (200 mg QD) puts most hepatically impaired patients in the target exposure range
➔ No dosing adjustment needed.

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Advantages

1. Provides control of a more relevant global error rate
   $\sup_{\Theta}$ P (incorrectly decide that no dose adjustments are needed) < 5%
2. Easier. No special computation needed to determine reference quantiles. Intersection-Union logic extends to testing multiple covariates.
3. Incentivizes sponsors to design studies that will result in narrow confidence intervals for covariate effects
4. Clarify the evidential role of the two fundamental types of simulation (fixed effects vs. population w/ BSV). This would create substantial operational efficiency; without this alignment we repeatedly re-invent the wheel

Closing Thoughts

1. MIDD rightly focuses on learning and not just confirming
   Nonetheless: it's learn **and confirm**. Grown-up MIDD *includes* confirmation
2. Statisticians know a lot about statistical confirmation and need to work with pharmacometricians on this (SxP SIG!)
3. More work needs to be done to clarify what should happen when we go down the BSV simulation branch of the decision path. E.g. would we even know if we need more data?
4. An area that could greatly benefit from estimand framework

https://sxpsig.github.io

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