

PKPD
~~PMx~~ and QSP: Compare, Contrast,
Converge, and Collide

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Convergent Evolution In Biology

“Animals all **face the same challenges**: finding enough to eat and surviving long enough to pass on their genes. While there are endless ways Nature has addressed these challenges, it **sometimes arrives at the same solution** in species that are only distantly-related. This phenomenon, called **convergent evolution**, can be seen in the similar body shape of fish and dolphins, the sharp spines of hedgehogs and porcupines, and the opposable thumbs shared by possums and primates.” <https://www.pbs.org/wnet/nature/blog/featured-creature-hummingbird-hawk-moth/>



Hummingbird Moth

<https://pxhere.com/en/photo/1112386>



Hummingbird

<https://pxhere.com/en/photo/1526375>

Convergent Evolution PKPD, Stats, and Systems Pharmacology

“[Quantitative Scientists] all **face the same challenges**: finding enough [data] and surviving long enough to pass [a life-changing drug along to our patients]. While there are endless ways [MIDD] has addressed these challenges, it **sometimes arrives at the same solution** in [departments] that are only [unnecessarily distant]. This phenomenon, called **convergent evolution**, can be seen in the similar [model types] of [PKPD] and [QSP], the sharp [splines] of [statistics] and [data scientists], and the opposable thumbs shared by [us all].”

<https://www.pbs.org/wnet/nature/blog/featured-creature-hummingbird-hawk-moth/> as modified by a moth/bird pharmacometrician



PKPD [shared](#)



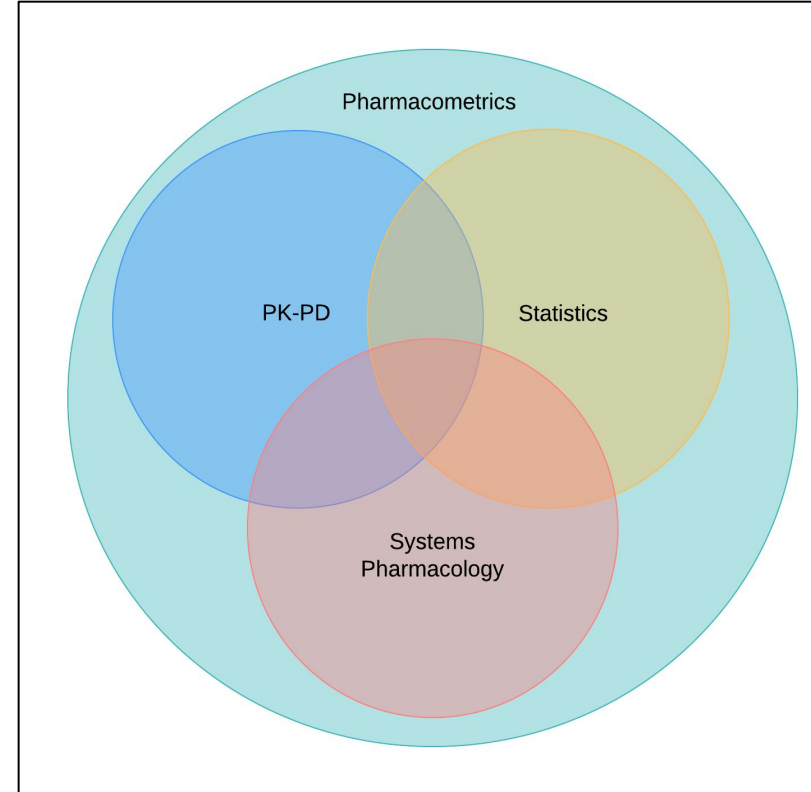
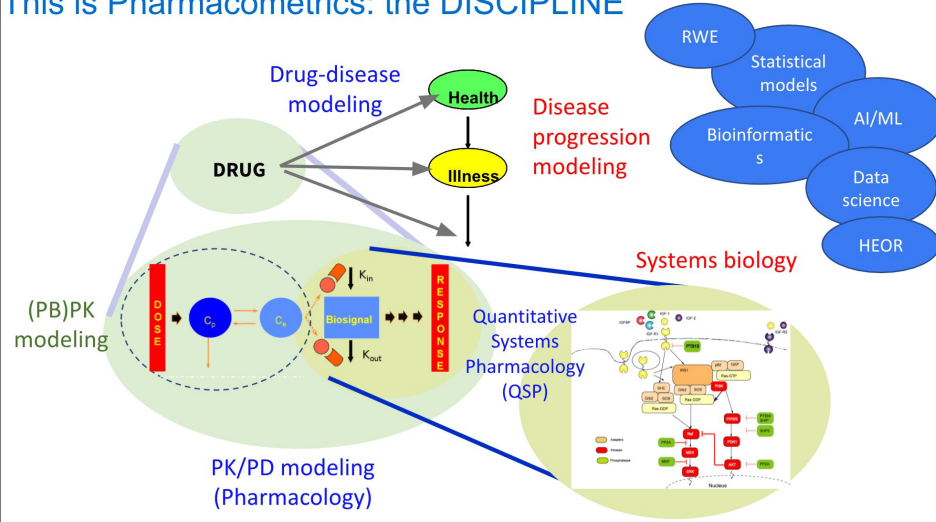
Statistics [ACoP10](#)



Steve Duffull [ACoP10](#)

Converge, Collide to a Cohesively Collaborative

This is Pharmacometrics: the DISCIPLINE



With This Balance There is Less of This...



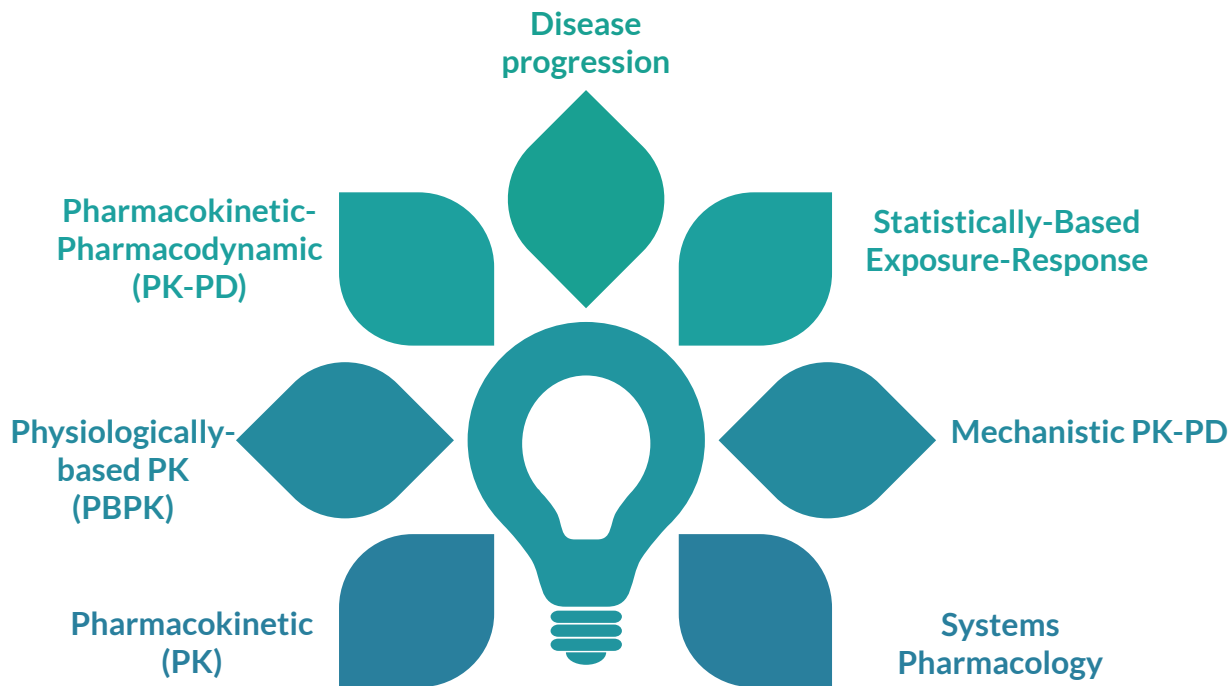
From [ACoP10, Orlando, FL October 2019](#) ... shared by Stacey T.

With This Balance And More of This...



From [ACoP10, Orlando, FL, October 2019](#) ... shared by Stacey T.

With This Balance and So Many Modeling Approaches How to decide which one(s) to use?



Get Started Using Question-Based, Model-Informed Drug Development

Define the Problem / Question

“Whoever best describes the problem is the one most likely to solve it”

– Dan Roam

Defining the Questions

- What fraction of the treatment population?
- What's the target product profile?
- What dose is necessary for efficacy?
- Is toxicity a concern at this dose?
- Are we better than the competitors?
- Will this trial succeed?
- Should We Invest Further in this Target or Compound?

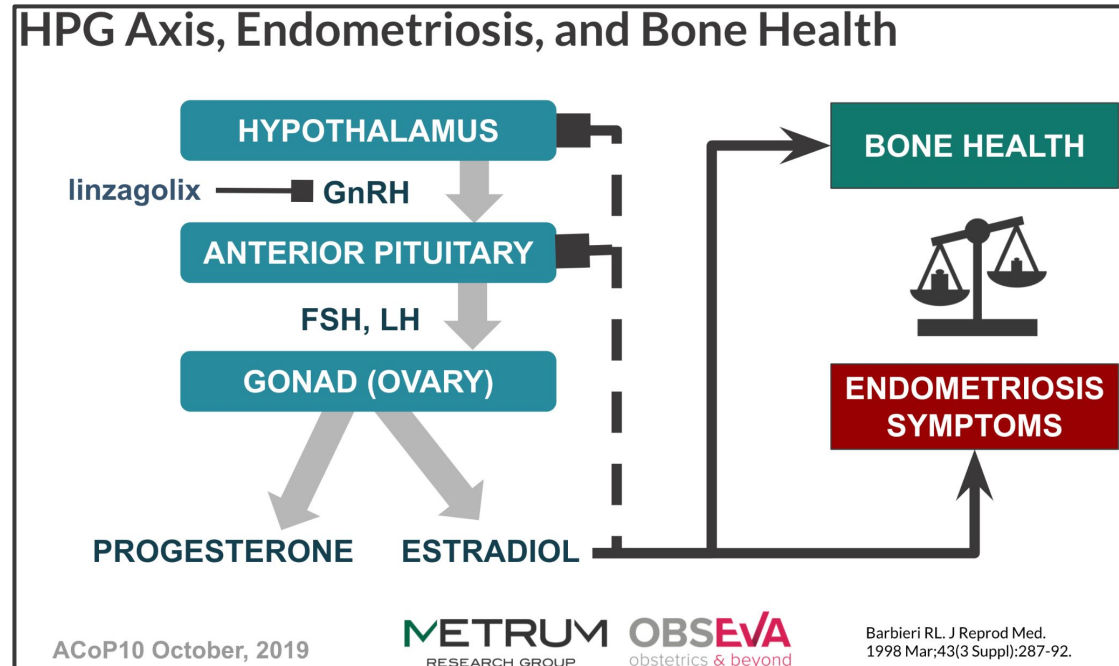


An Example: Which Approach(es) Fit the Question?

- Linzagolix - an oral **GnRH** receptor antagonist in development for the treatment of **endometriosis** and **uterine fibroid** symptoms

Background

- How this drug works



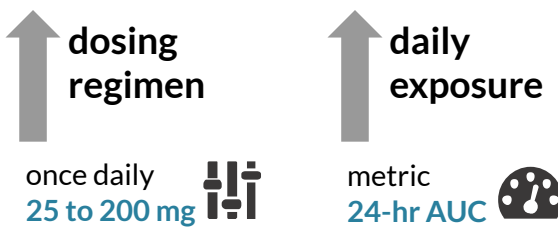
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Key Question

- Which dose range should be studied in Phase 3?
- Goals:
 - select doses that balance safety and efficacy
 - have a high probability of meeting target profile

Pohl et al. A model-based analysis to guide gonadotropin-releasing hormone receptor antagonist use for management of endometriosis. Br J Clin Pharmacol.2021;1–13.



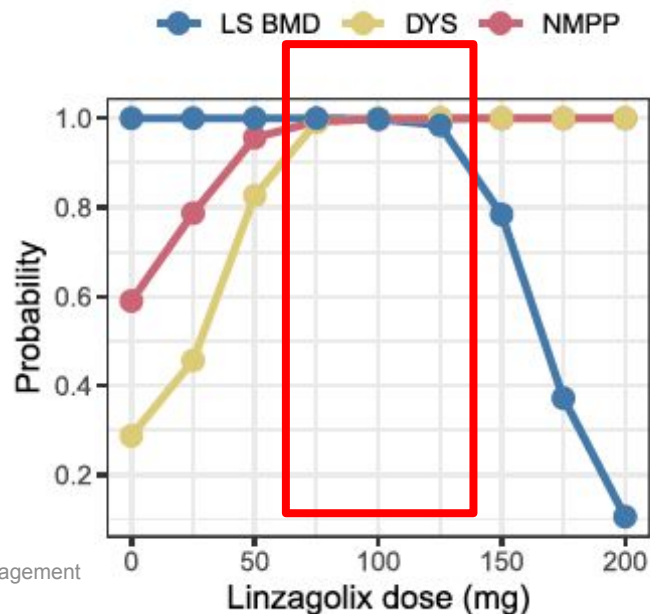
Recommending a decision

The team identified clinically meaningful targets for BMD loss and pain reduction.

E2 in 20 - 50 pg/mL window a reasonable target

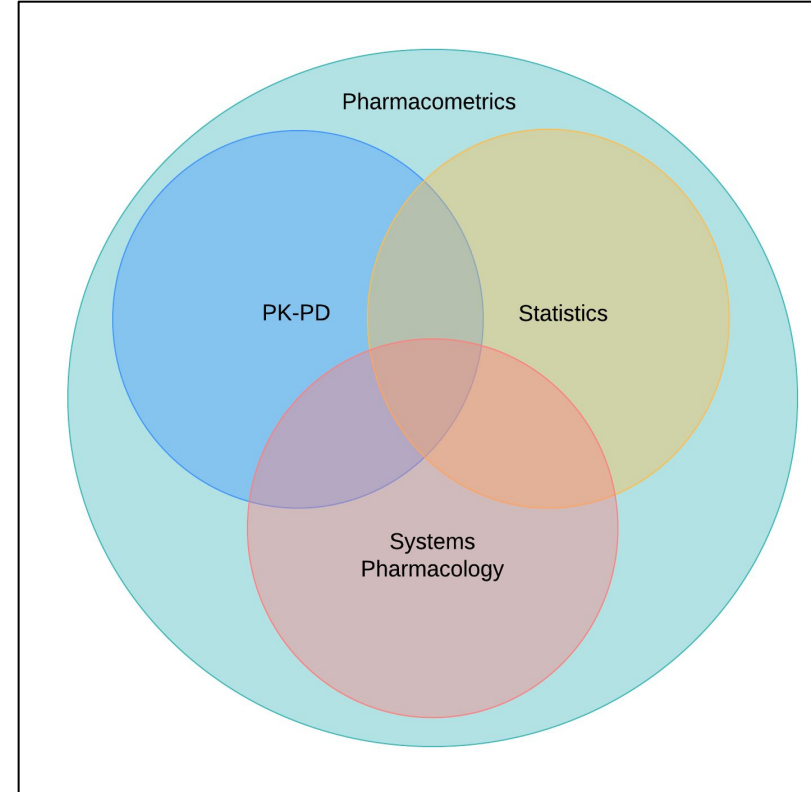
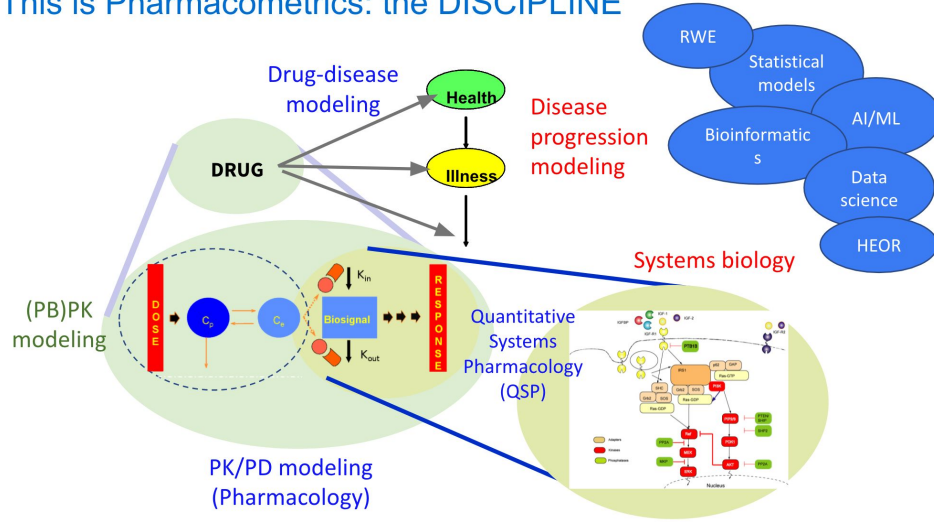
- Linzagolix once daily doses between 75–125 mg daily were expected to meet endometriosis-associated pain, efficacy, and BMD loss targets...

Through M&S, the team identified a range of doses that are predicted to meet these criteria.



Converge, Collide to Cohesively Collaborative

This is Pharmacometrics: the DISCIPLINE



Stephen Duffull – Data and systems modelling leapfrog towards clinical care



Steve Duffull [ACoP10](#)