ASCPT

FROM MOLECULE TO PATIENT

ASCPT 2019 ANNUAL MEETING

QSP Applications in Drug Discovery and Development & Decision-Making --Regulatory Science Applications

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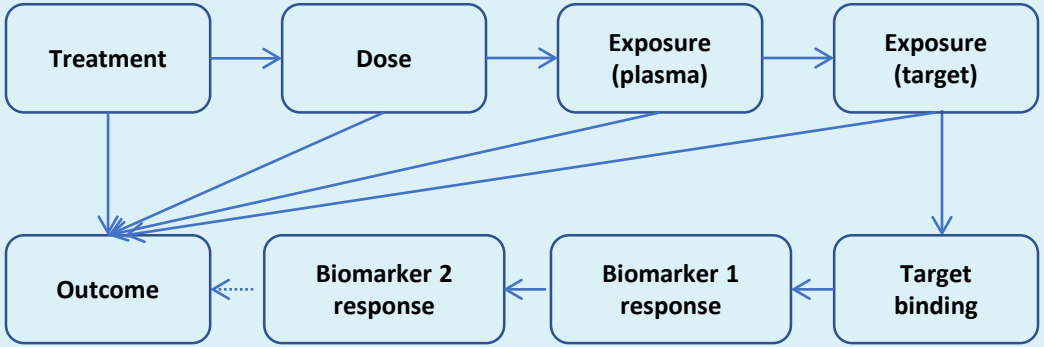
Disclaimer: My remarks today are my own personal views and do not represent those of the FDA

Key Messages

- Mechanistic models with different levels of complexities have been applied to help various regulatory decisions
- Highly mechanistic QSP models are generally used to support early discovery and drug development decisions
- Supportive evidence for decisions related to late phase trials/endpoints
- More experience is being accumulated

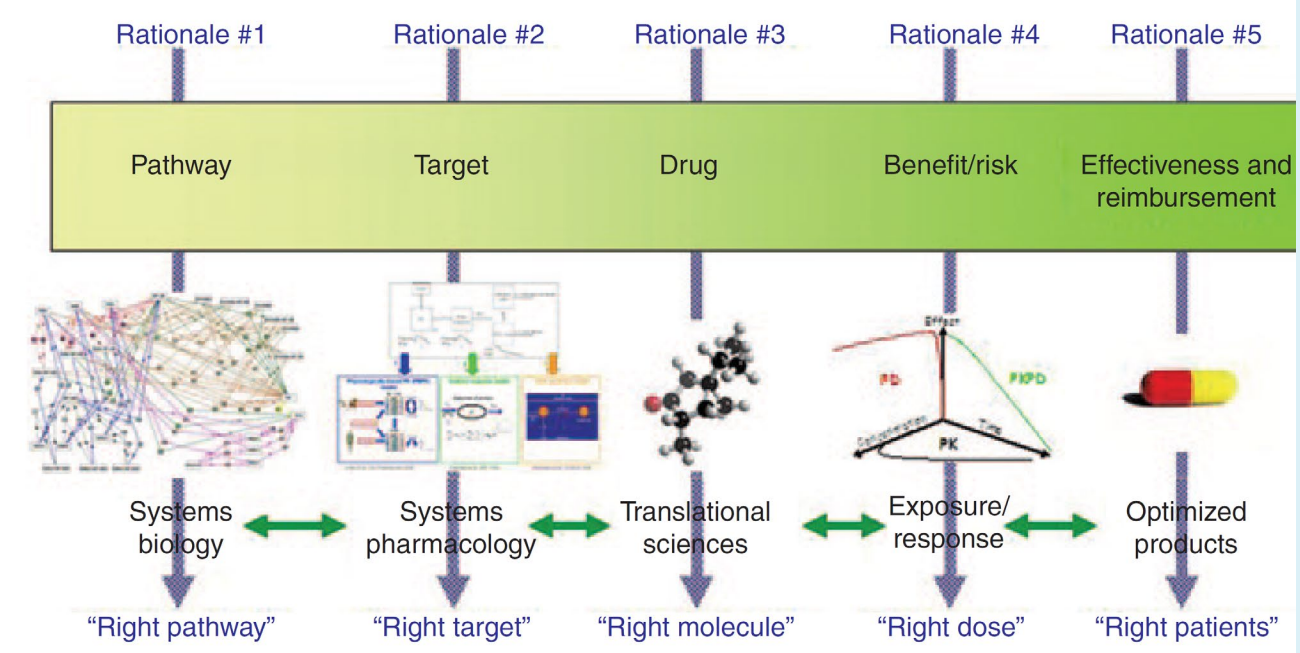
Different Levels of Mechanistic



- The more mechanistic the analysis is, the more complex the model is and the more data/information is needed
- Knowledge gap between biomarker responses and clinical endpoints

Commentary on Fit-For-Purpose Models for Regulatory Applications.
Yaning Wang, Shiew Mei Huang, J Pharm Sci. 2019 Jan;108(1):18-20

QSP in Drug Discovery and Development



Model-Based Drug Development: A Rational Approach to Efficiently Accelerate Drug Development, PA Milligan, et al., Clin Pharmacol Ther. 2013 Jun;93(6):502-14

Role of Mechanistic Models
Semi-mechanistic to highly mechanistic

- Dose-exposure-biomarker-clinical response
  - Efficacy/safety prediction
  - Interpolate or extrapolate dose or dosing regimen
  - Dose adjustment for specific population/condition
  - Combination therapies
  - Subgroup
  - Dose modification/individualization
  - …

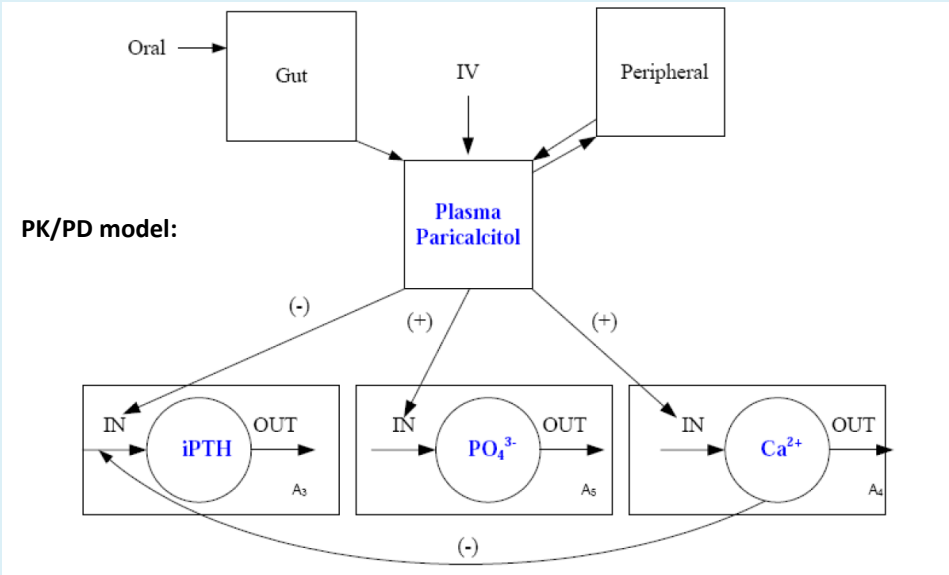
Case 1: Paricalcitol

- Indication: Secondary hyperparathyroidism associated with chronic renal failure
- 3 failed trials due to unacceptable rates of hypercalcemia
- 4th trial (design developed based on modeling and simulation from failed trials) showed improvement as predicted
- Due to the change in guideline for hypercalcemia evaluation (lower threshold), previously acceptable rate is now unacceptably high, especially in a sub-population
- Do we ask for a new trial or apply the modeling and simulation method to derive an optimal dosing regimen that balances effectiveness and safety for all patients without another trial?

Approach

- Evaluate various clinical “what-if” questions using PK/PD simulation based on a semi-mechanistic model
- Derive optimal dosing recommendations for all patients based on PK/PD simulation to balance efficacy and the new safety requirements
- Is this a QSP model?

PK/PD model:



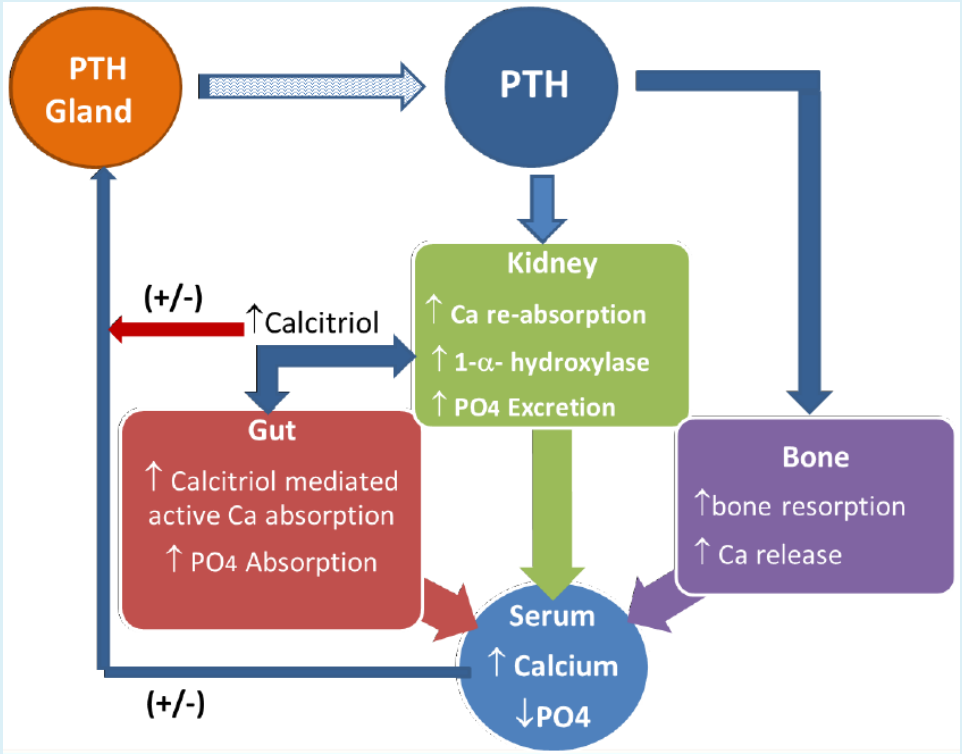
Summary of Case 1

- Paricalcitol capsules approved for Stage 5 CKD in hemodialysis (HD) and peritoneal dialysis (PD) patients without additional trials
- A lower initial dose compared to that studied based on baseline disease severity
- An entry criteria for treatment to minimize incidence of hypercalcemia
- A dose titration strategy based on current disease severity and safety
- All these PK/PD simulation based information is included in the product label

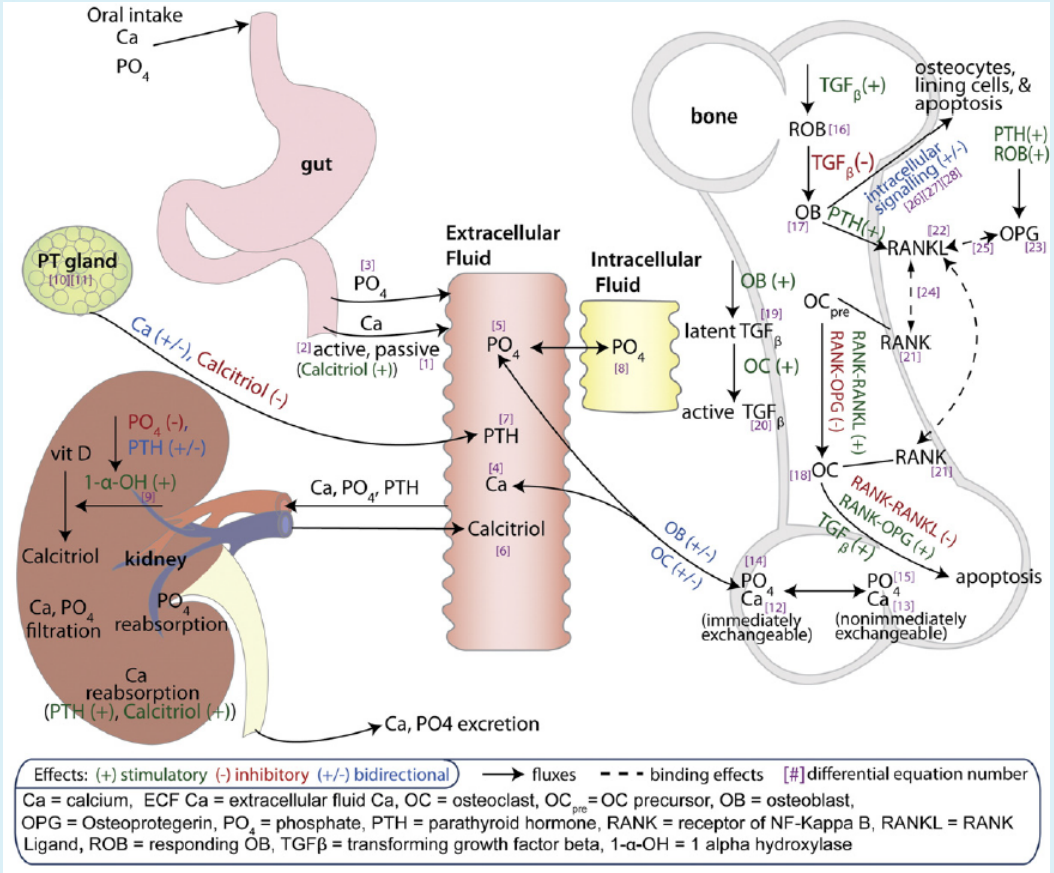
Case 2: Natpara

- Recombinant human parathyroid hormone
- Indicated for the long-term treatment of Hypoparathyroidism as a replacement for endogenous parathyroid hormone
- Hypoparathyroidism is a rare endocrine deficiency that is characterized by absent or inappropriately low circulating parathyroid hormone (PTH) levels, in association with hypocalcemia, hyperphosphatemia, and hypercalciuria
- Once daily dosing regimen proposed by the sponsor is not adequate to control hypercalciuria

Parathyroid Hormone Mechanism of Action

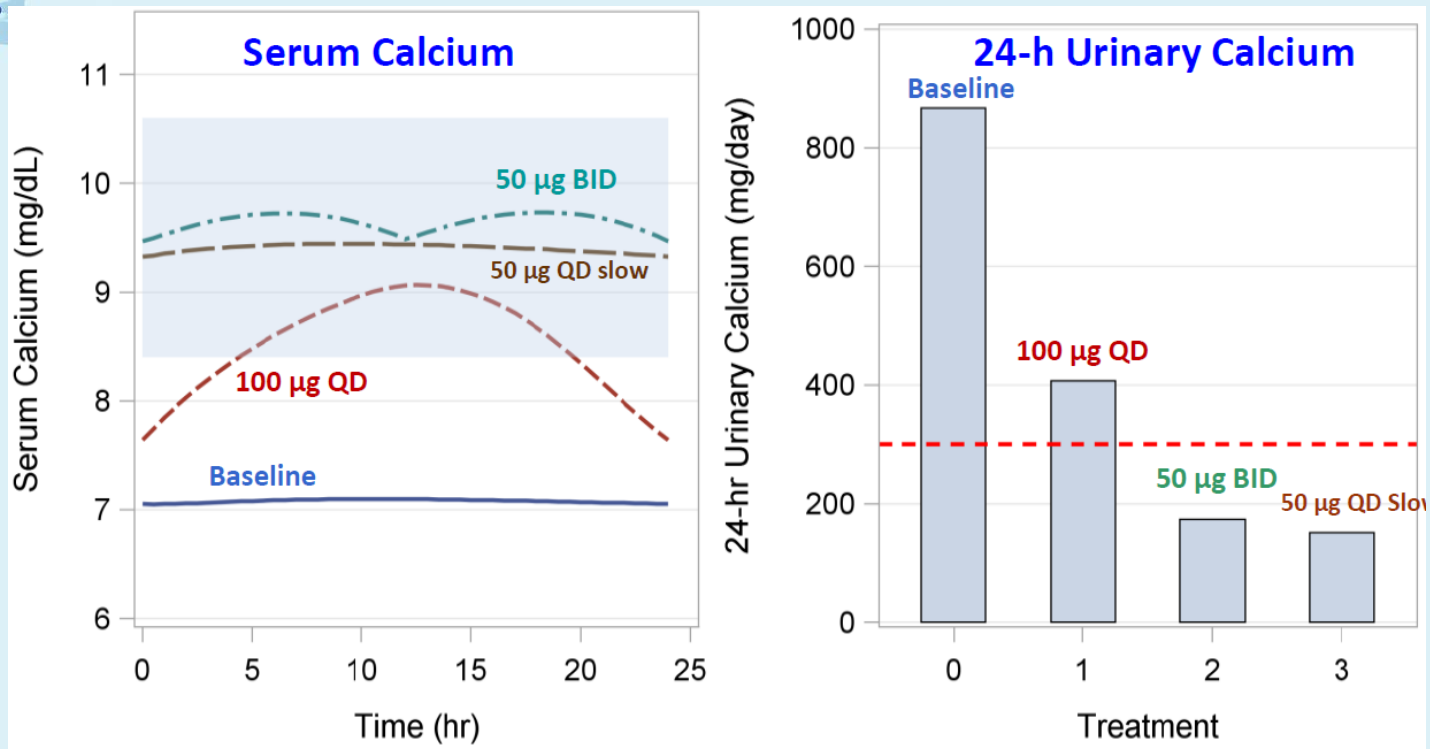


Schematic of the Systems Biology Model



Peterson MC and Riggs MM. Bone. 2010 Jan;46(1):49-63

Altering Regimen (QD to BID) or Release Profile Controls Hypercalciuria While Maintaining Normocalcemia



http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm386727.htm

Summary of Case 2

- Observed PK time course in light of PD time course suggests more frequent dosing.

- QSP simulations provided the expected outcomes of altering the dosing regimen on hypercalciuria and thus supported a post-marketing dose-optimization trial.

- Clinical data were needed to confirm the predicted results.

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/

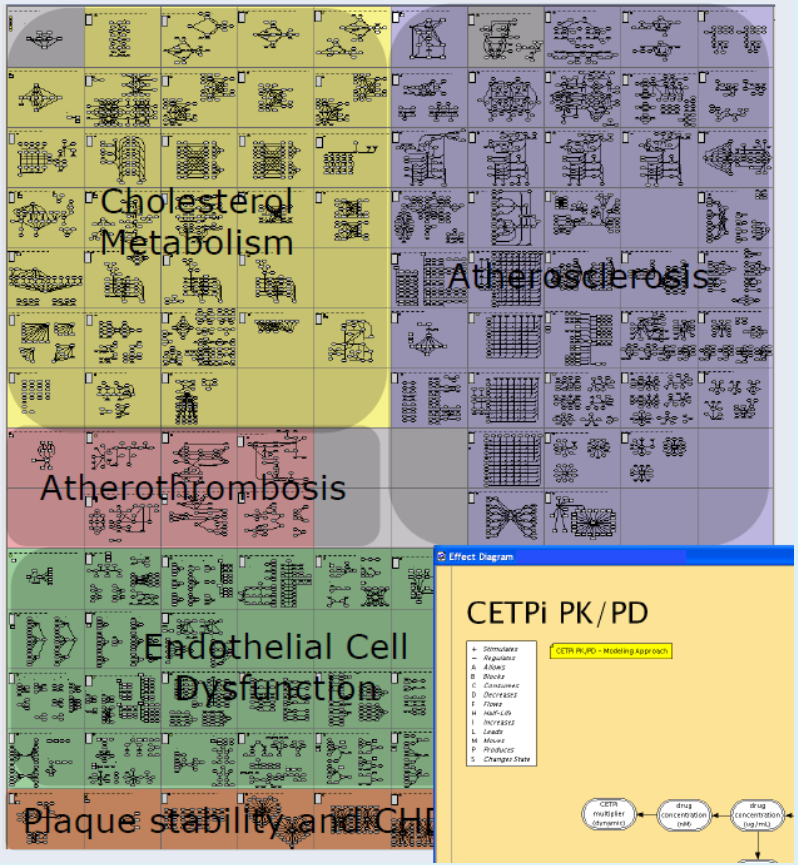
Case 3: CETP Inhibitor

- A CETP inhibitor is a member of a class of drugs that inhibit cholesterylester transfer protein (CETP)
- Drugs in this class substantially increase HDL ("good cholesterol"), lower LDL ("bad cholesterol"), and reverse the transport of cholesterol.
- Torcetrapib failed in 2006 due to excess deaths in Phase III clinical trial (ILLUMINATE)
- Off-target effect on blood pressure was believed to be partially responsible for the increased death rate
- A systems pharmacology project was initiated to understand and quantify the integrated effects

https://en.wikipedia.org/wiki/CETP_inhibitor

Barter PJ, et al., N Engl J Med. 2007 Nov 22;357(21):2109-22; Johns DG, et al., Drugs. 2012 Mar 5;72(4):491-507

Cardiovascular PhysioLab® Platform



Summary of Case 3

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- A mechanistic computer model of coronary heart disease (CHD) physiology
- Quantitatively predict cholesterol metabolism and plaque growth in the coronary artery over time through the dynamic simulation of relevant biological pathways
- Published data for torcetrapib (60 mg qd), dalcetrapib (600 mg qd) and anacetrapib (100mg qd) were used to calibrate the model
- Statistical methodologies are used to translate predicted changes in circulating lipids and plaque characteristics to predictions of CHD risk
- Dalcetrapib (Roche) simulations do not predict any clinically meaningful changes in hazard (0.99±0.20)
  - dal-OUTCOMES stopped in May 2012 due to lack of clinically meaningful efficacy
  - Hazard ratio: 1.04 (95%CI: 0.93-1.16, p=0.52)
- Despite an additional decrease in LDL-C and the largest increase in HDL-C, anacetrapib (Merck) simulations predict a very small reduction in hazard (0.96±0.28)
  - Rate ratio: 0.91 (95%CI: 0.85-0.97, p=0.004)

Karim Wahba et al, Clinical trial simulations of dyslipidemic patients in a mechanistic model of cardiovascular disease predict little impact on CHD events by CETP inhibitors, American Heart Association (AHA) annual meeting, 2011
Gregory G. Schwartz , et al., N Engl J Med 2012; 367:2089-2099 November 29, 2012, http://www.nejm.org/doi/full/10.1056/NEJMoa1206797#t=article
The HPS3/TIMI55–REVEAL Collaborative Group, N Engl J Med 2017; 377:1217-1227September 28, 2017, http://www.nejm.org/doi/full/10.1056/NEJMoa1706444

Case 4: Drug Induced Liver Injury Model

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- A cooperative R&D agreement (CRADA) between Entelos/Hamner Institutes and the FDA's Center for Drug Evaluation and Research (CDER)
- To develop a PhysioLab platform for drug-induced liver injury, or DILI, to allow scientists to predict how drugs and chemical agents might damage the liver in humans and rats
- Multiple publications at different stages of the model development
- Later evolved into DILI-sim Initiative

https://www.genomeweb.com/informatics/hamner-entelos-co-develop-drug-induced-liver-injury-simulation-software
https://www.fda.gov/ScienceResearch/ucm122820.htm
https://c-path.org/wp-content/uploads/2013/10/MS-workshop-12-session-III-03-Paul-Watkins.pdf

Application in Drug Development

- Solithromycin, a new compound proposed for the treatment of community acquired bacterial pneumonia
- Application was discussed at the advisory committee meeting (2016)
- Major safety issue: liver toxicity
- DILI-sym was applied to explain the mechanism and the observed liver toxicity in clinical trials
- "…the Complete Response Letter (CRL) stated that the FDA determined the risk of hepatotoxicity had not been adequately characterized"

https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM527690.pdf
https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM528874.pdf
http://investor.cempra.com/releasedetail.cfm?ReleaseID=1005708

FDA's Comments on DILIsym Based Conclusion

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Computational Modeling of Solithromycin Associated Risk: Analysis Issues & Limitations

- …a firm conclusion that solithromycin is not associated with a risk for clinically serious idiosyncratic hepatotoxicity cannot be drawn
- Separately, in the simulation of solithromycin dosing to treat CABP, known mechanisms and pathways that appear to contribute to severe liver injury associated with macrolides and ketolides are not addressed by the model.
- Among these, immuno-allergic reactions and hypersensitivity pathways tied to DILI that have been identified with members of these drug groups have not been incorporated into the simulation analysis.
- A somewhat surprising additional unexplained gap in the analysis submitted by DILISym Services is the absence of the parallel testing of telithromycin hepatotoxicity in a simulated CAP population.
- The sponsor has put forth a so far unproven argument that despite their pharmacological and structural similarities as ketolides, solithromycin is marked by a substantially lower potential to cause severe hepatotoxicity than telithromycin.

https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM527690.pdf

Case 5: Dosing Frequency Change (X to Y)

- **Can QSP analysis be used support the dosing frequency change from X to Y?**
- **Application Specific Discussion (Not Policy):**
  - ***Can only serve as supportive evidence***
  - ***The main evidence supporting the approval of the proposed dosing regimen are based upon similar exposure between X and Y***
  - ***Consideration of the exposure-response relationships***
  - ***Challenge focuses both on gap between QSP and clinical data to answer questions as well as model validation***

QSP in Drug Development: The IND Stage

- An increasing number of QSP submissions:
  - Target Selection
  - Synergy between two drugs
  - Target Receptor Occupancy
  - First In Human Dose Selection
  - Dose Justification for early phase clinical trials

Summary

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Acknowledgments

- Division of Pharmacometrics
- Office of Clinical Pharmacology
- Office of New Drugs
- Many sponsors

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THANK YOU

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Division of Pharmacometrics (DPM) /Office of Clinical Pharmacology (OCP) is Hiring!

- **Positions**
  - PBPK reviewer and Pharmacometrics reviewers
- **Responsibility**
  - Approve and label the drug product with particular attention to drug do sing at the individual and population levels.
  - Provide advice on trial design and development path decisions to sponsors.
  - Conduct research to create new knowledge based on the unique data available at the FDA (i.e. prior submissions) and literature to inform better regulatory decisions by the FDA and drug development decisions by sponsors
- **Minimum requirements**
  - An earned Ph.D. or other professional doctorate in PKPD, Statistics, Engineering, Clinical Pharmacology, or relevant fields
  - Hands-on experience with modeling and simulation software (e.g. NONMEM, SAS, Splus/R, Trial Simulator, WinBUGs, Phoenix, Monolix, GastroPlus, PKSIM, SimCYP, etc.)
  - Good knowledge of PK/PD modeling principles and statistics.
  - Good communication and interpersonal skills
  - Candidates should have continuous residence in the US for the last 3 years.
- **How to apply**
  - Send your CV to Yaning.Wang@fda.hhs.gov or Hao.Zhu@fda.hhs.gov