Return on Investment on the Utilization of Systems Pharmacology and Pharmacometrics in Drug Development for Rare Diseases: Challenges and Opportunities

ACCP Workshop
September 26, 2015

Modeling & Simulation: Filling the Knowledge Gap in Rare Diseases

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Metrum Research Group

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Disclosures

- M.R. Gastonguay and C.J. Godfrey are salaried employees of Metrum Research Group

- Metrum Research Group is a contract research service provider to multiple pharma/biotech companies (specific names bound by confidentiality). Several of these companies develop therapeutics for rare diseases.

Acknowledgements

- CJ Godfrey
- Janelle Hajjar
- Industry and academic collaborators

Learning Objectives

- Recognize some of the knowledge gaps typical to rare disease drug development programs
- Understand the opportunities, challenges, and limitations associated with applying modeling and simulation to integrate knowledge in rare disease drug development
- Recognize future potential of modeling and simulation to support knowledge-building in rare disease drug development

Overview

- A Hypothetical Scenario
- Knowledge Gaps
- Possible Solutions with Modeling and Simulation
- Learning from Specific Examples
- Limitations
- Opportunities

The Scenario

You've just been hired for your dream job!

- Venture capital-funded company (ProntoROI)
  - Shoe string budget
- Senior leader in clinical pharmacology and pharmacometrics
  - A department of 1
- Company has intense focus
  - One drug candidate
  - Pushing to confirmatory Phase 3 efficacy trial asap

- Company is committed to developing drugs for rare diseases
  - You have no experience in issues of rare disease drug development

Hypothetical Rare Disease

- In-born error of metabolism
  - Genetic basis
- Patient population spans from infant to adult
  - Infants have most severe and possibly fatal form
- Disease does not affect any single ethno-racial group
  - Global development planned
- Disease defined as ultra-rare
  - prevalence <6,000 US

Knowledge Gaps

- New chemical entity (bioengineered enzyme replacement)
- No control arm in trials conducted so far
- Limited efficacy dose-response data (2 active doses)
- Formulation process changes
- Differences in disease genotype & disease severity phenotype
- Total clinical trial experience to date has included 55 subjects
  - PK, safety, tolerability, biomarkers
  - Proof of concept on efficacy endpoint

Your Goals

- Select dose & regimen for Phase 3 trial
- Define any dose adjustment in pediatric patients vs. adults
- Deliver a dossier for registration in multiple regions:
  - Rigorously characterizes benefit & risk (B/R) of the new entity
  - Demonstrates that B/R is consistently realized in the (sub)populations of interest
- "Approval of all drugs – for both rare and common conditions – must be based on demonstration of substantial evidence of effectiveness in treating or preventing the condition and evidence of safety for that use"

21 CFR 314.126
Guidance for Industry, 2015, Rare Disease: Common Issues in Drug Development. DRAFT

http://www.usnews.com/news/articles/2014/02/11/study-income-gap-between-young-college-and-high-school-grads-widens

The Goal, more generally…

- Let's consider that what we are building is a response surface…
  - Some amalgamation of safety and efficacy
  - Relates dose, intrinsic and extrinsic factors, disease progression and severity and phenotype to safety and efficacy
- Knowledge of the response surface allows us to:
  - adjust the factors we can control (e.g. dose)
  - given the factors we can't control (disease phenotype)
  - achieve the optimal sweet spot of highest probability of response tempered by probability of adverse events

The Challenge

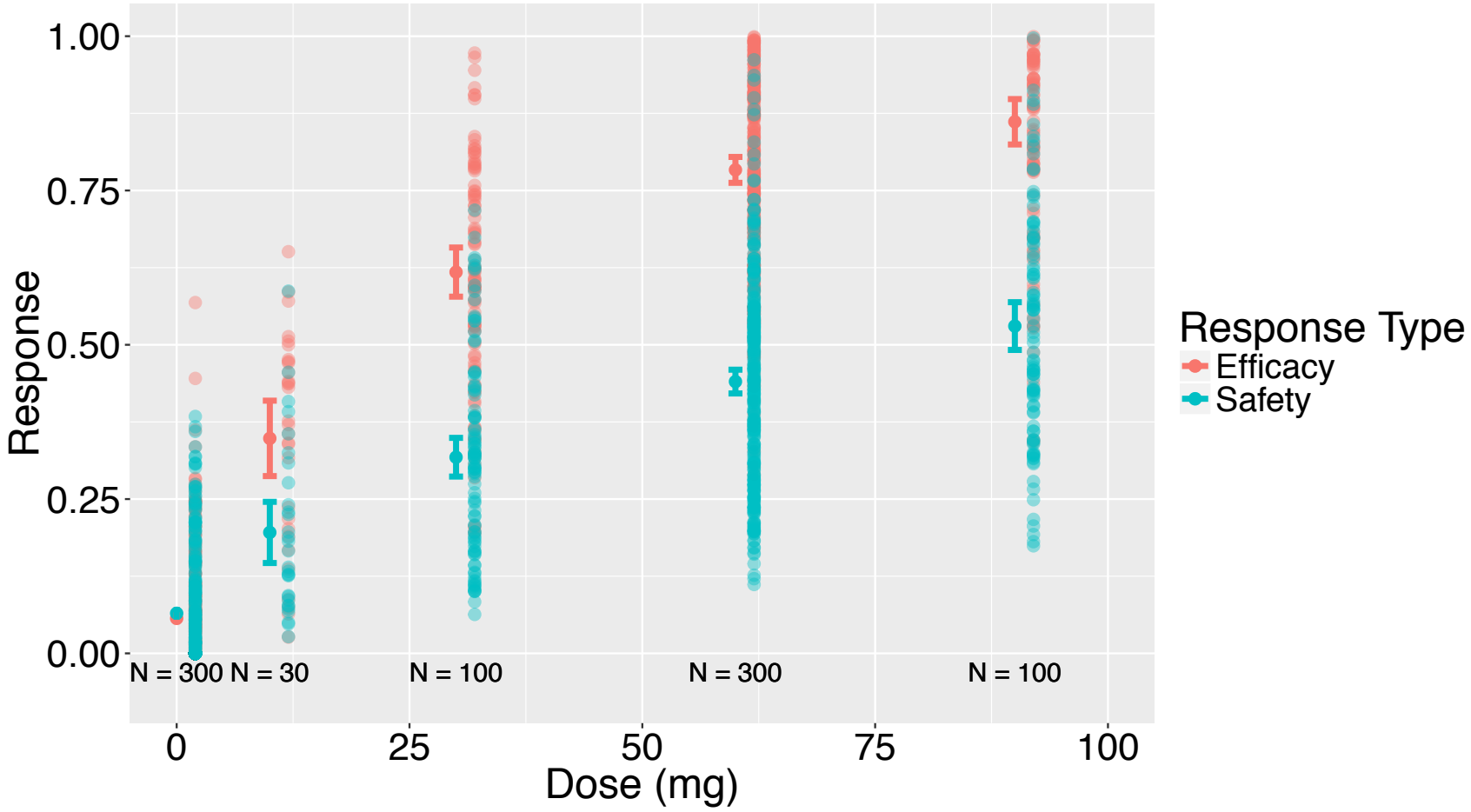
- Achieve the goal despite the most significant hindrance:

  Small number of patients
  Low incidence, low prevalence

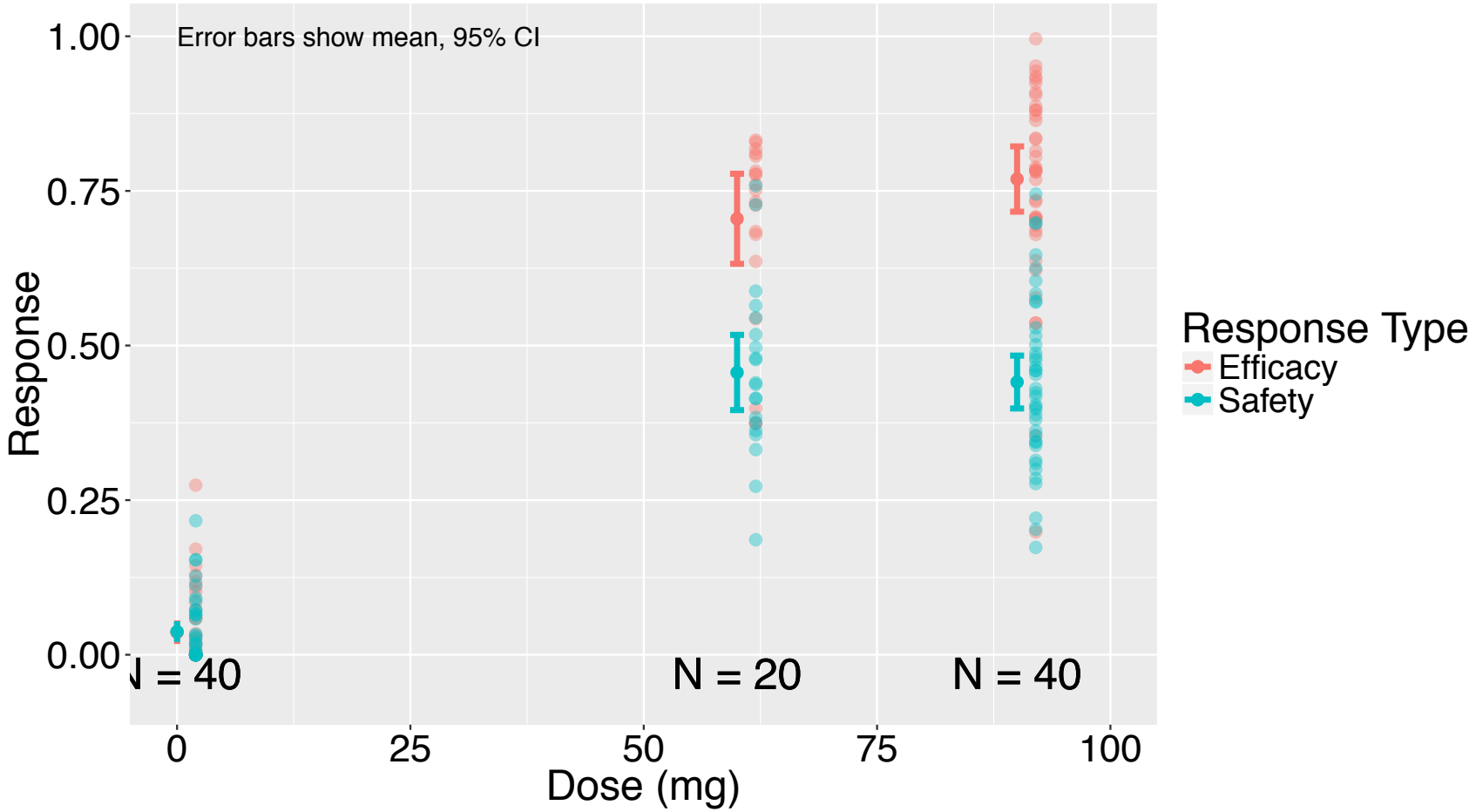
- Many of the other hurdles of drug development for rare diseases find their significance in this one fact

- Our "response surface" has lots of holes…

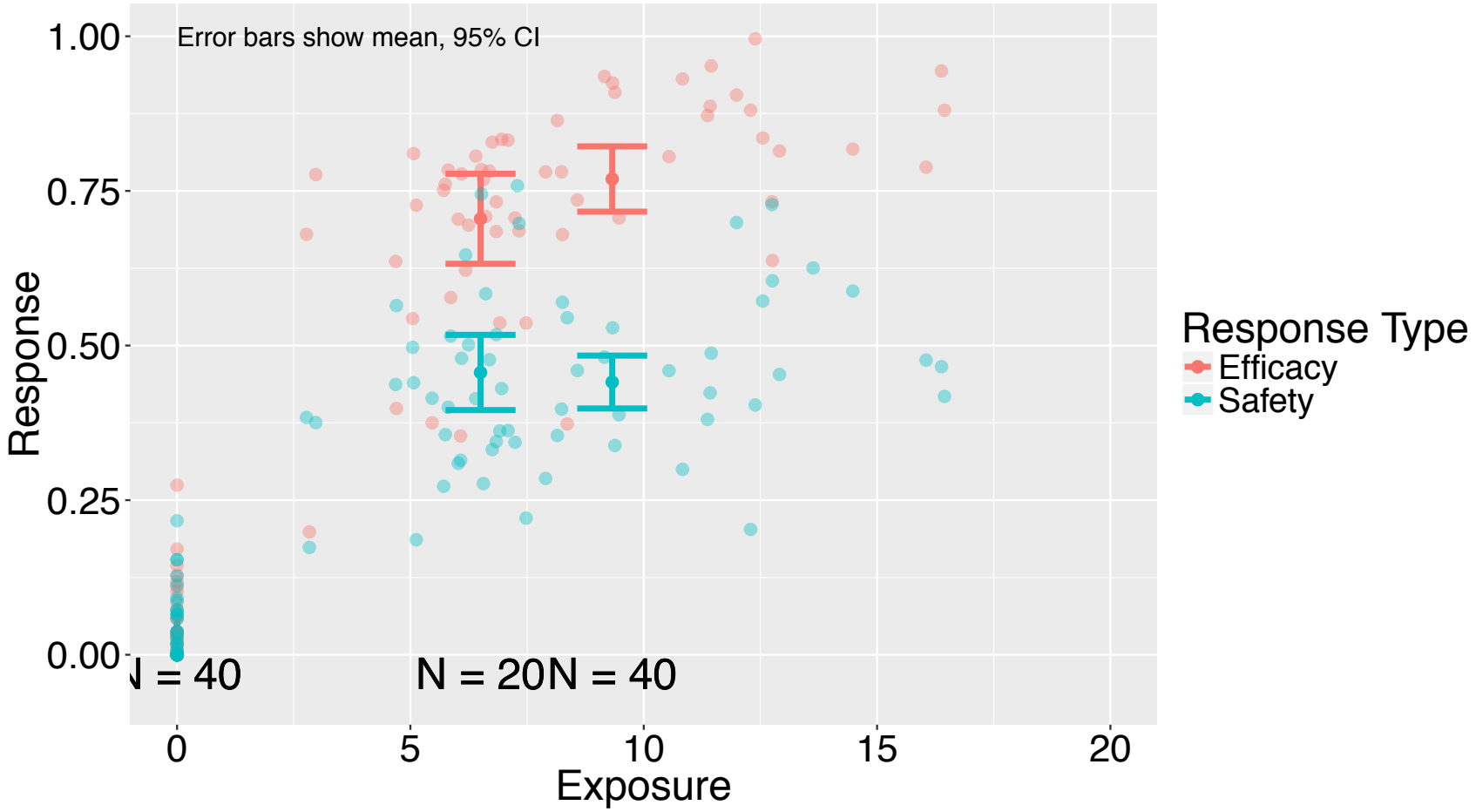
Dose-Response Data in Common Disease



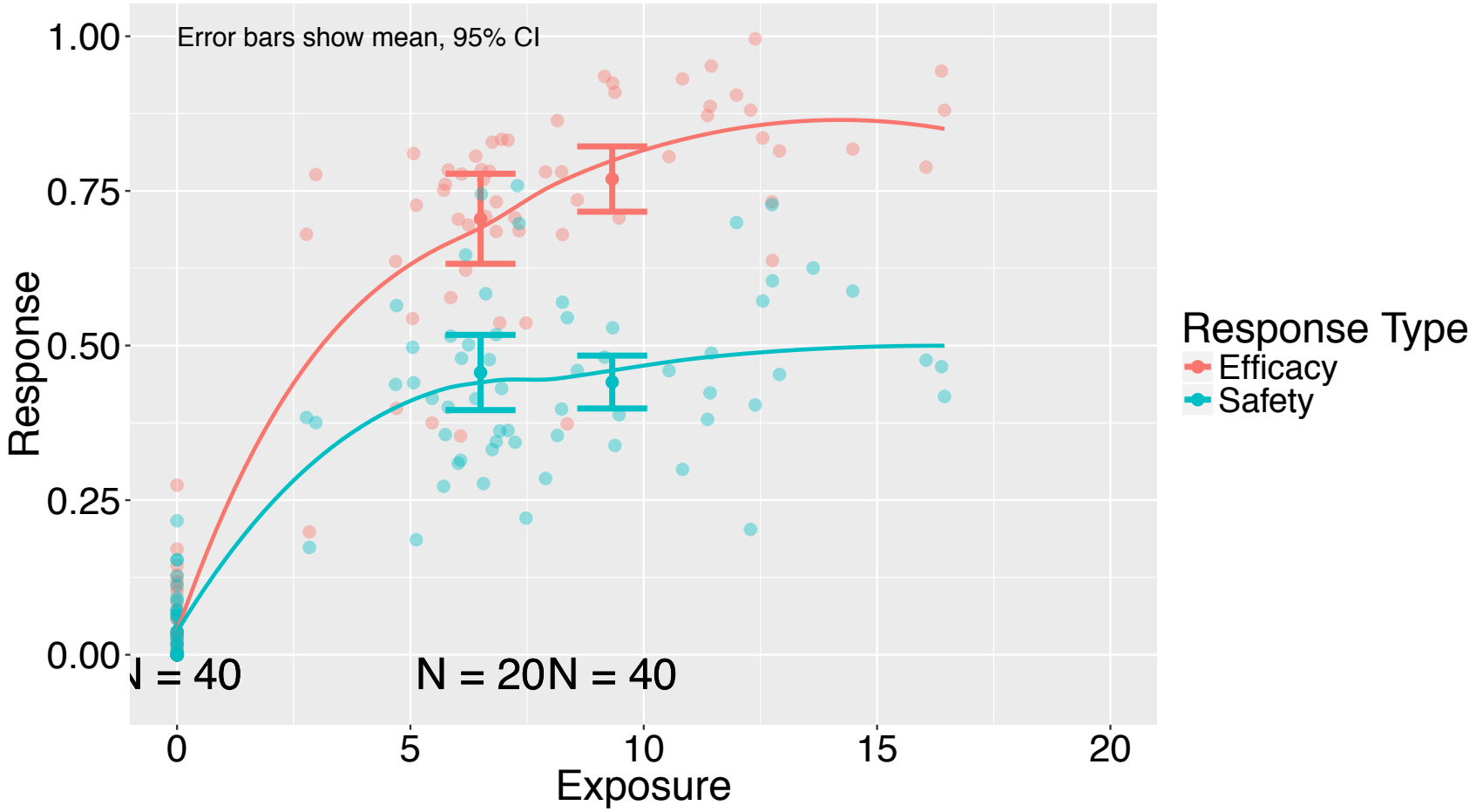
Dose-Response Data in Ultra-rare Disease



Exposure-Response in Ultra-Rare Disease



Exposure-Response in Ultra-Rare Disease



The Hurdles

The hurdles to a well-defined response surface for treatment of a rare disease **are the same as for common diseases** but are more difficult to overcome due to the paucity of data.

We must answer the same questions…

But we need methods that will efficiently integrate the limited data and fill in the knowledge gaps…the holes in our response surface

http://www.usnews.com/news/articles/2014/02/11/study-income-gap-between-young-college-and-high-school-grads-widens

The Hurdles

- Disease heterogeneity
  - Genotypes, phenotypes, clinical types
  - Stages, severity, aggressiveness, manifestations
  - Disease progression
- Complexity of affected populations
  - Pediatrics, adults
  - Race, ethnicity, sex, age

The Hurdles

- Assessment of Efficacy
  - Identification and calibration of meaningful and quantifiable clinical endpoints
  - No control group, reference treatment, or placebo
  - How to incorporate data from historical controls
  - Collecting the right data at the most informative times
  - Impact of factors such as anti-drug antibodies
  - Timing and extent of dose adjustment

The Hurdles

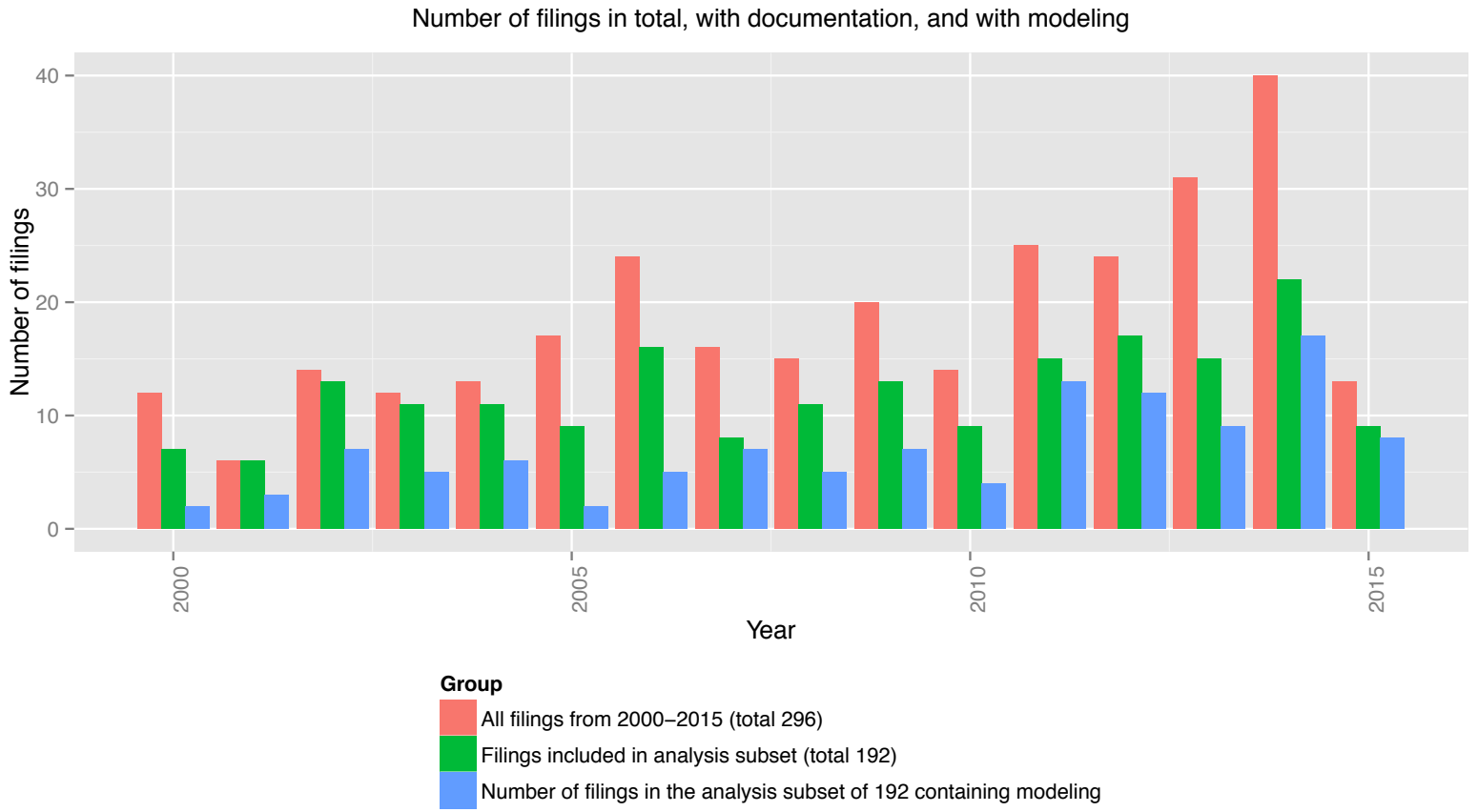
- Assessment of Safety
  - Obtaining sufficient data to understand incidence and severity of adverse events
  - Knowledge of the margin of safety
  - Timing, extent, and duration of dose adjustment

The Hurdles

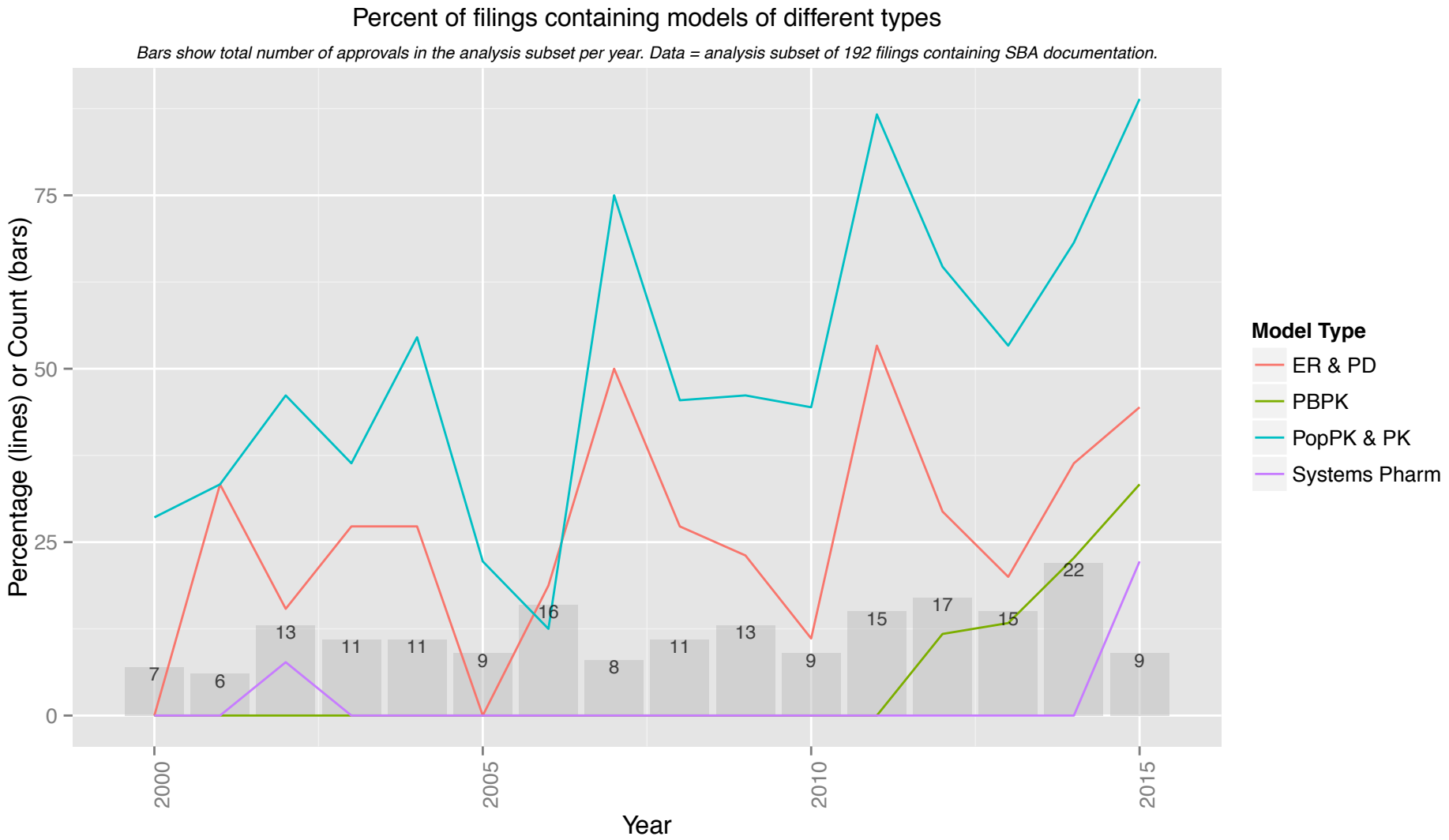
- Diminished opportunity for application of learn-confirm paradigm
- Typical constellation of intrinsic and extrinsic factors to be evaluated
- Infeasibility of 'standard' Phase 1-3 development program

Learning from Other Rare Disease Programs

- Explore applications of modeling and simulation to integrate knowledge in other rare diseases

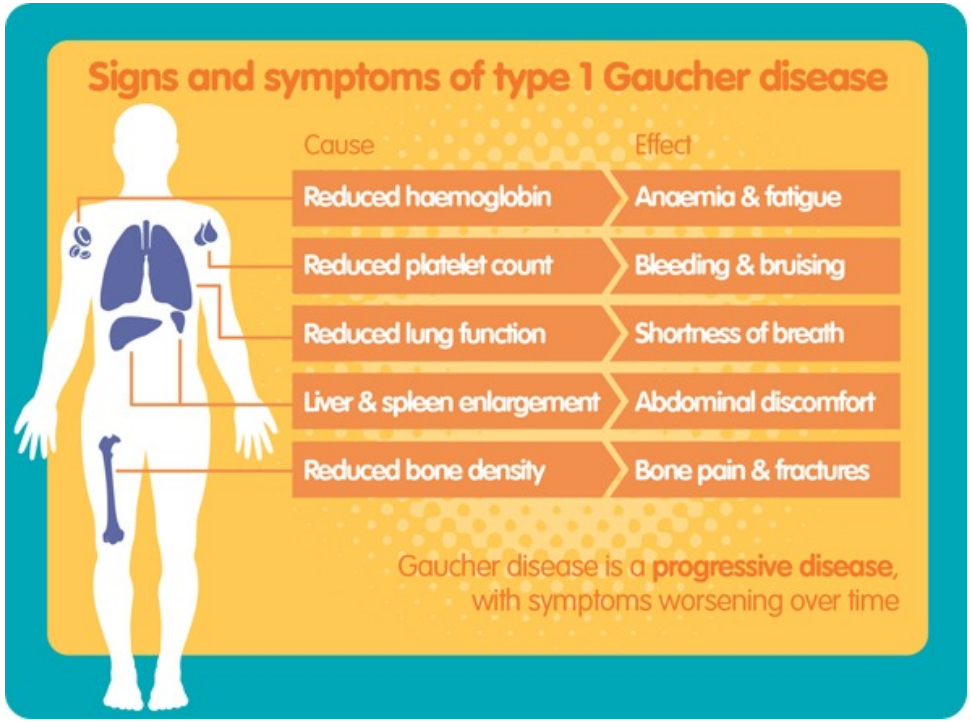


Types of M&S in Rare Disease Drug Development



Type 1 Gaucher Disease

- Type 1 (non-neuronopathic)
- Rare, serious, and potentially fatal, genetic disorder
- Lysosomal storage disorder; lipid accumulation in cells
- Genetic deficiency or absence of glucucerebrosidase
- 1/40,000 globally (1/855 Ashkenazi Jewish heritage)



http://www.news-medical.net/news/20140930/Gaucher-disease-an-interview-with-Dr-Clement-Olivier-Shire.aspx

http://ghr.nlm.nih.gov/condition/gaucher-disease

Eliglustat for Type 1 Gaucher Disease

Knowledge Gaps

- CYP2D6 and CYP3A4 drug interactions
- Impact of CYP phenotype on exposure
- Effects of other covariates on exposure
- Impact of exposure on QTc

Filling the Gaps

- PBPK model development
- PBPK simulation
- Population PK modeling
- Concentration-QTc modeling

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205494Orig1s000ClinPharmR.pdf

Eliglustat for Type 1 Gaucher Disease

Knowledge Gaps

- CYP2D6 and CYP3A4

QTc

Filling the Gaps

- PBPK model

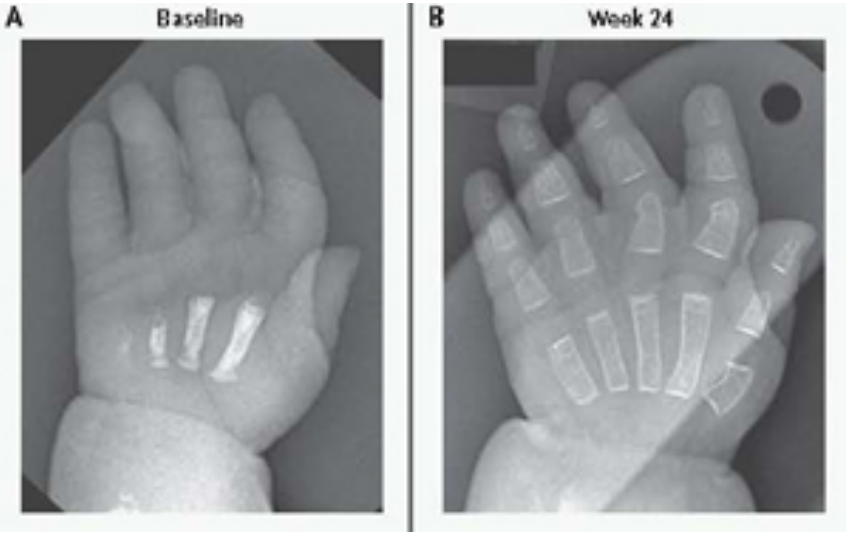
KEY LEARNINGS:

- Exploring multiple doses and regimens in different metabolizer phenotypes is not practical in rare diseases
- Model based simulation was used to explore impact of different doses and regimens on exposure by phenotype
- M&S scenarios were requested by regulatory reviewer

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205494Orig1s000ClinPharmR.pdf

Hypophosphatasia

- Rare, serious, and potentially fatal, genetic disorder
- Cause: loss-of-function mutation(s) in the gene encoding the tissue-nonspecific isoenzyme of alkaline phosphatase.
- Poor bone calcification
- Severity of disease is related to age of disease onset.



Whyte MP, Greenberg CR, Salman NJ, Bober MB, McAlister WH, Wenkert D, Van Sickle BJ, Simmons JH, Edgar TS, Bauer ML, Hamdan MA, Bishop N, Lutz, RE, McGinn M, Craig S, Moore JN, Taylor JW, Cleveland RH, Cranley WR, Lim R, Thacher TD, Mayhew JE, Downs M, Millan JL, Skrinar AM, Crine P, Landy H. Enzyme-replacement therapy in life-threatening hypophosphatasia. *New England Journal of Medicine*. Vol 366. Pages 904 – 913. March 8, 2012.

- Prevalence of severe disease in North America 1/100,000, globally - unknown

https://rarediseases.org/rare-diseases/hypophosphatasia/

Hypophosphatasia

Knowledge Gaps

- Dose and regimen selection
- Pediatric dose adjustment
- Multiple PD and efficacy endpoints
- Formulation / process changes

Filling the Gaps

- Population PK modeling
- PK-PD modeling for each endpoint
- PK-PD based simulation
- Model based assessment of extrinsic factors on PK and response
- Model based bridging to global regions

ASBMR2015 SU0380. Pradhan RS[1], Gastonguay MR[2], Gao X[1], Monteleone JPR[1], Fisher J[2], Godfrey CJ[2], Dirks NL[2], Melian A[1], Thompson DD[1], Lathia CD[1]
Exposure-Response Modeling and Simulation to Support Evaluation of Efficacious and Safe Exposure and Dose Range for Asfotase alfa in Patients with Hypophosphatasia

Hypophosphatasia

Knowledge Gaps

- Dose and regimen
  changes

Filling the Gaps

- Population PK modeling
- Model based bridging to global regions

KEY LEARNINGS:

- In ultra-rare diseases, patients are often enrolled sequentially in multiple clinical trials.
- Use model-based methods to integrate data from each individual across studies.
- Learn about PK-PD relationships and disease progression from within-subject changes in design/conditions across multiple endpoints.

ASBMR2015 SU0380. Pradhan RS[1], Gastonguay MR[2], Gao X[1], Monteleone JPR[1], Fisher J[2], Godfrey CJ[2], Dirks NL[2], Melian A[1], Thompson DD[1], Lathia CD[1]
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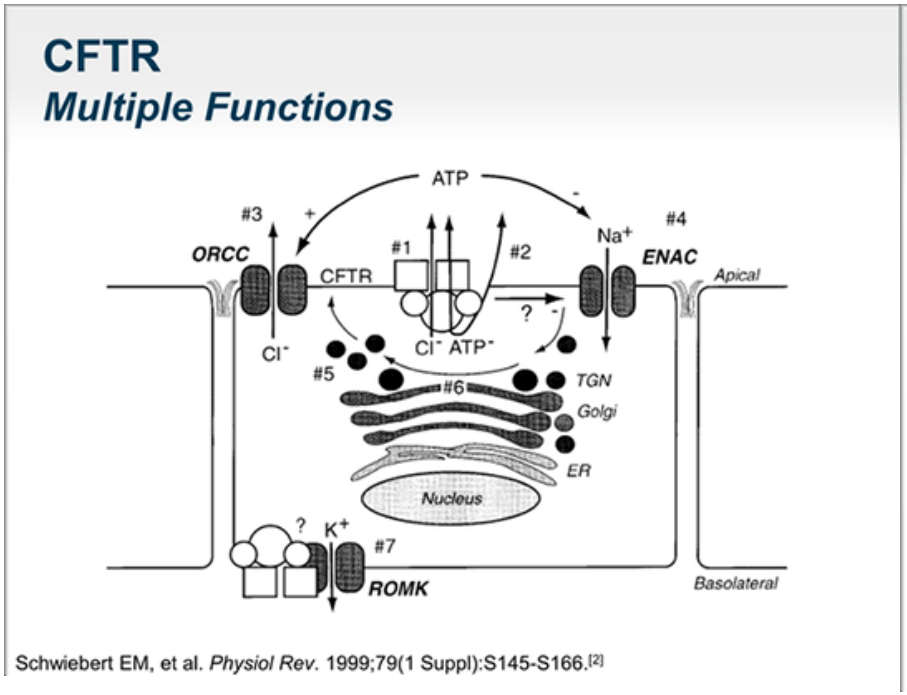
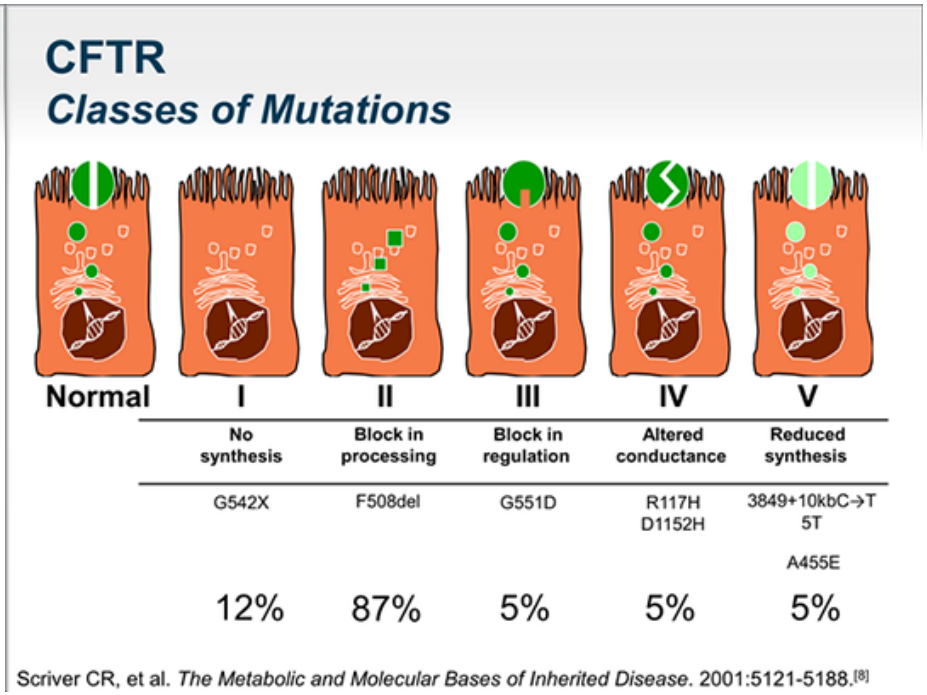
Cystic Fibrosis





http://www.medscape.org/viewarticle/806649_transcript

- 70,000 globally (~90% F508del) but some genotypes are much more rare
- Corrector and potentiator therapeutics

Cystic Fibrosis

Knowledge Gaps

- Pediatric dose
- Efficacy of combination of corrector and potentiator
- Dose selection for monotherapy or combination therapies
- Dose-response in rare genotypes

Filling the Gaps

- Population PK modeling
- PK-PD modeling for efficacy endpoints

http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203188lbl.pdf
http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206038Orig1s000lbl.pdf
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM446193.pdf

Cystic Fibrosis

Knowledge Gaps

- Pediatric dose
- Dose-response in rare genotypes

Filling the Gaps

- Population PK modeling

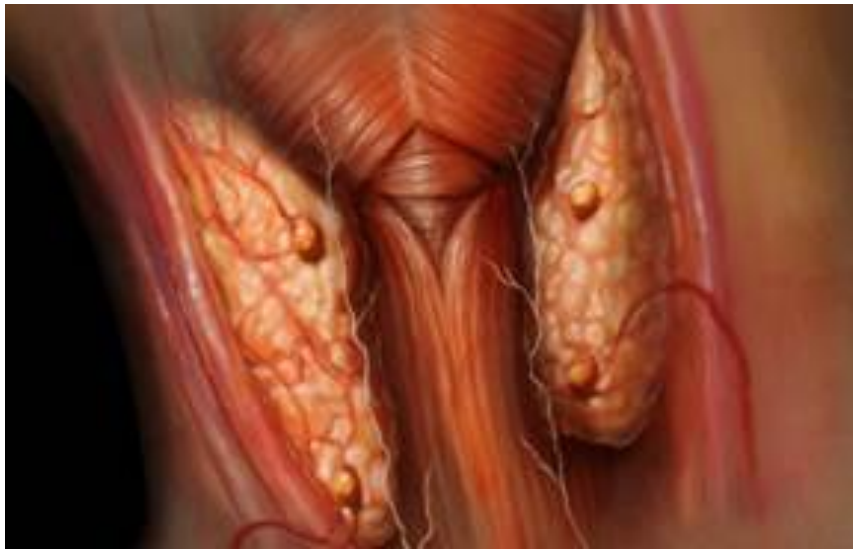
KEY LEARNINGS:

- In ultra-rare genotypes, dose-response study designs are a challenge
- Does the dose-response relationship translate across genotypes?
- Consider creative methods for dose-ranging studies (Bayesian adaptive methods, MCPMod, etc.)
- Assess impact of uncertainty in dose-response translation through model-based simulation

http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203188lbl.pdf
http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206038Orig1s000lbl.pdf
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM446193.pdf

Hypoparathyroidism

- Types: aquired, congenital, autoimmune, ideopathic
- Lack of PTH or poor utilization of PTH
- Symptoms due to low plasma calcium
- Muscle weakness, numbness, spasms, tetany, and seizures (rare)

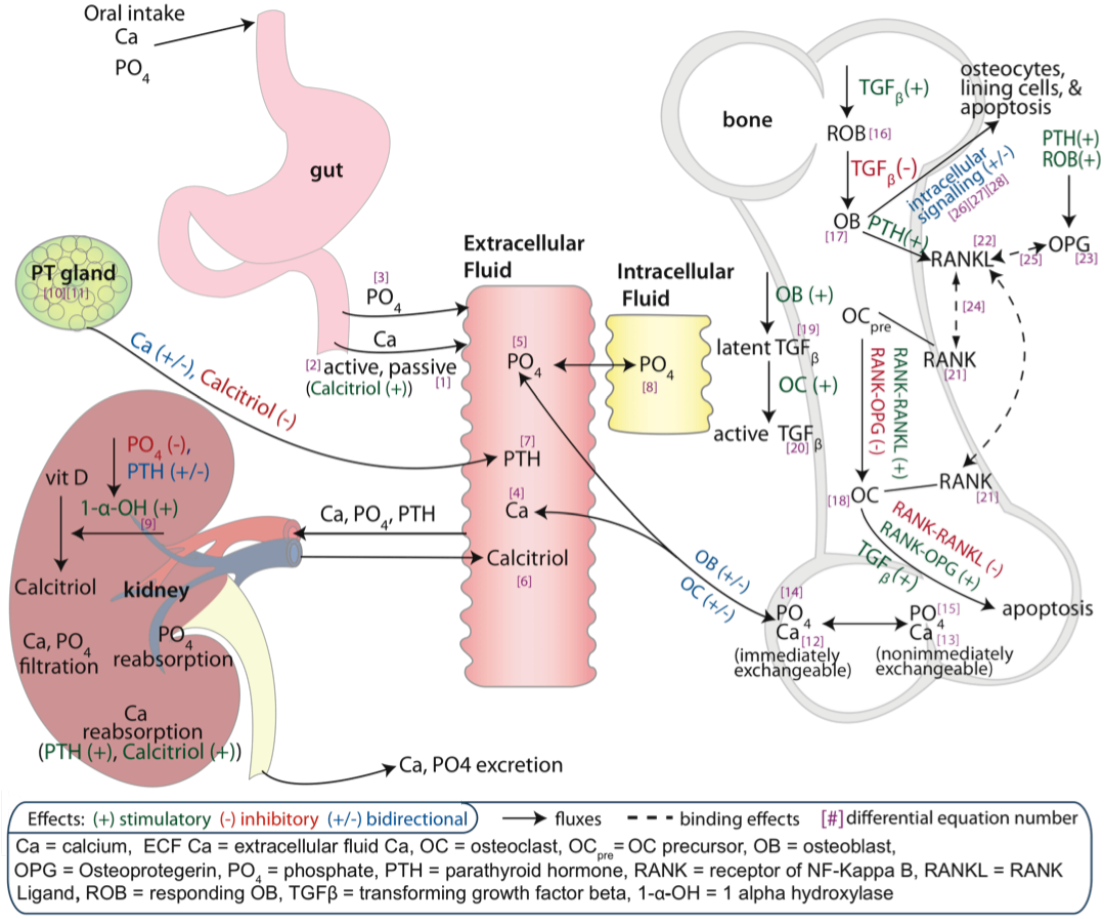


http://www.endocrinologyadvisor.com/bone-metabolism/fda-approves-natpara-for-hypocalcemia-in-hypoparathyroidism/article/394343/

- Wide range of disease severity

https://rarediseases.org/rare-diseases/hypoparathyroidism

Systems Pharmacology Modeling

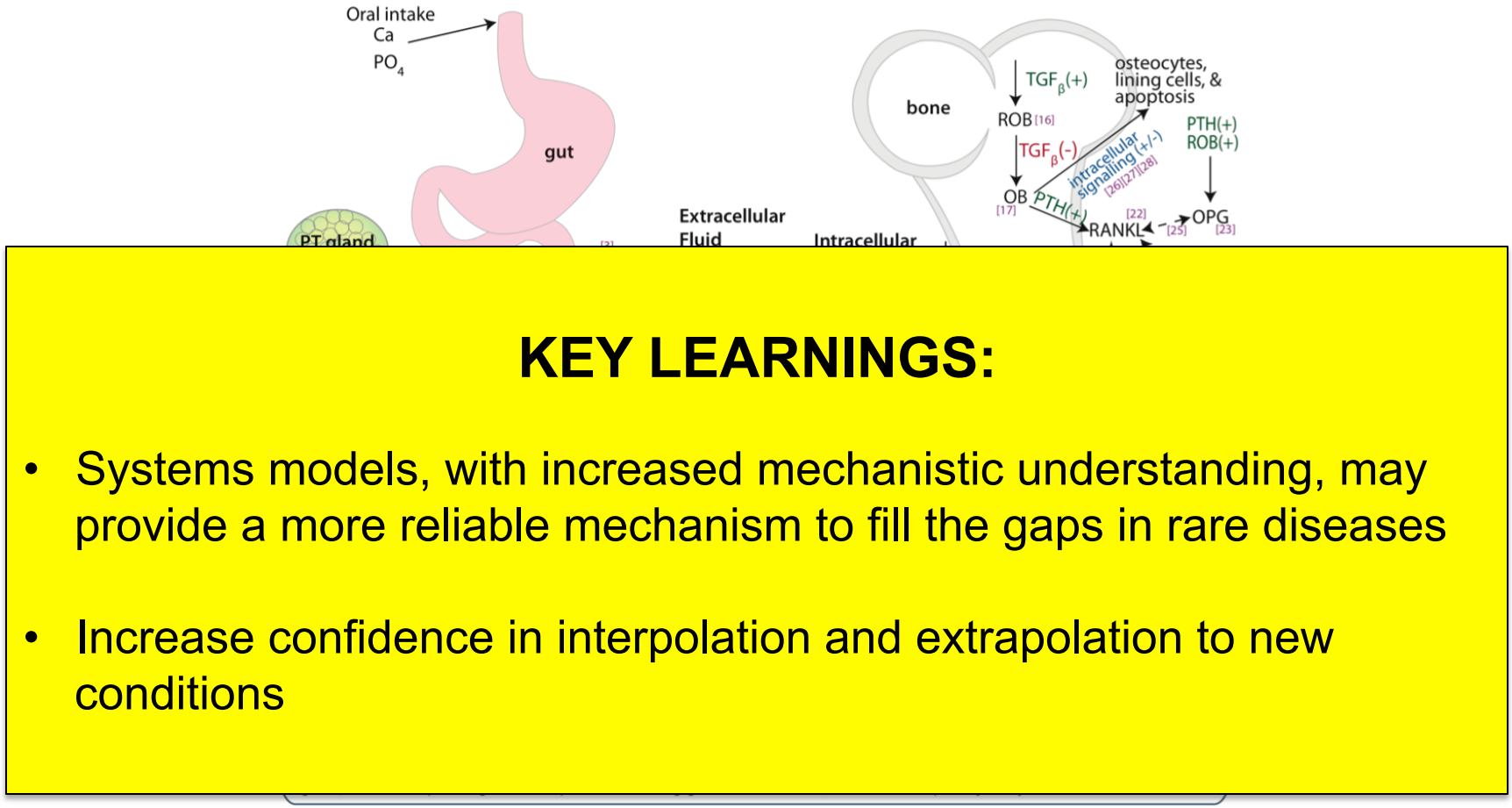


Bioengineered parathyroid hormone: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM413617.pdf

A physiologically based mathematical model of integrated calcium homeostasis and bone remodeling. Mark C. Peterson and Matthew M. Riggs. Bone 46 (2010) 49–63.

Multiscale Physiology-Based Modeling of Mineral Bone Disorder in Patients With Impaired Kidney Function. Matthew M. Riggs, Mark C. Peterson, Marc R. Gastonguay. J Clin Pharmacol. Volume 52, Issue S1, pages 45S–53S, January 2012

Systems Pharmacology Modeling



KEY LEARNINGS:

- Systems models, with increased mechanistic understanding, may provide a more reliable mechanism to fill the gaps in rare diseases
- Increase confidence in interpolation and extrapolation to new conditions

Bioengineered parathyroid hormone: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM413617.pdf

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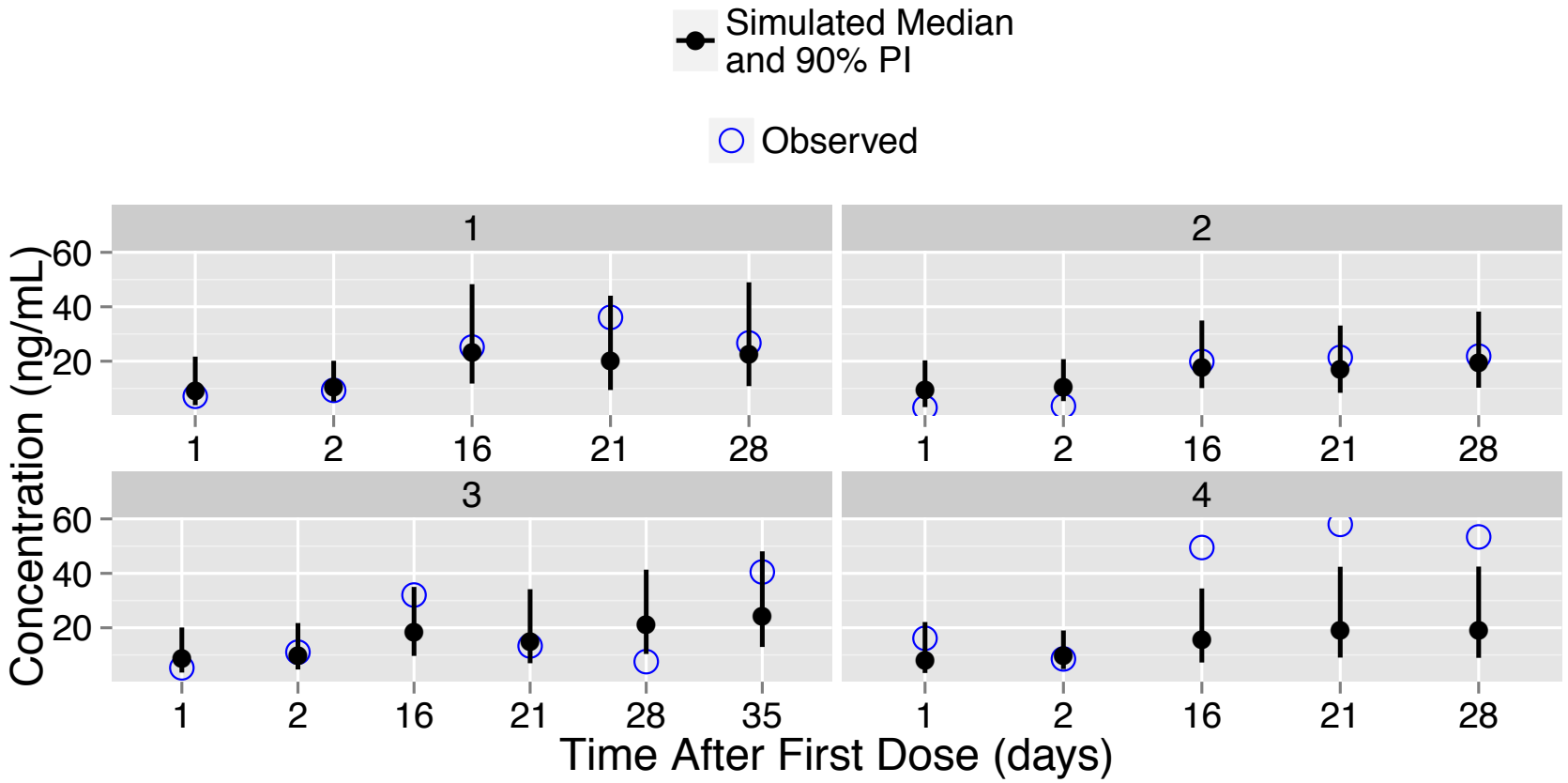
Technical M&S Challenges

Small populations, small sample size:

- Poor precision of model parameters
- Difficult to characterize sources of variability with small N
- Often requires model-based interpolation or extrapolation
- Increased probability of selection bias with stepwise covariate modeling
- Data themselves do not provide a robust characterization of population variability
  - How to perform simulation-based model checking?

Individual-Specific Posterior Predictive Check

- Strategy for model checking
- Establish bridging to other populations/regions



Multiple Gaps

http://www.bzzagent.com/blog/wp-content/uploads/2013/06/Gap-In-Mountain.jpg

M&S Can Only Go So Far

- Use M&S to uncover or quantify additional knowledge gaps & deficiencies
- Given these uncertainties, M&S provides informed guidance on how to fill the gaps with new studies/ designs

http://www.bzzagent.com/blog/wp-content/uploads/2013/06/Gap-In-Mountain.jpg

Filling Multiple Knowledge Gaps

- New data collection driven by M&S-informed study designs
- Integrate knowledge sources with M&S

http://www.bzzagent.com/blog/wp-content/uploads/2013/06/Gap-In-Mountain.jpg

Modeling and Simulation …

… is **essential** for successful development and registration of drugs for rare and ultra-rare diseases

… **creates and integrates knowledge and understanding** not necessarily achievable by traditional methods

… **quantifies uncertainty** and assesses the impact of uncertainty on study design, treatment, and approval decisions

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