Application of Global Systems Analysis (GSA) for Simulation of Oral Absorption

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PSE Advanced Process Modelling Forum

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Pfizer WORLDWIDE RESEARCH & DEVELOPMENT

SCIENCE FOR LIFE-CHANGING IMPACT

Factors Influencing Oral Absorption

Formulation & process properties

Drug properties (Molecular and Material)

P_{app} or logD, MW

MW, pKa, S_0, LogP

Dosage Form

DISINTEGRATION
DISPERSION

API particles

DISSOLUTION

NUCLEATION/ GROWTH

Kn, n

H_2O

CO_3^{2-} K_{sp} H^+

PERMEATION

Na^+

API^+ ⇌ API

Cl^-

Bile OH^-

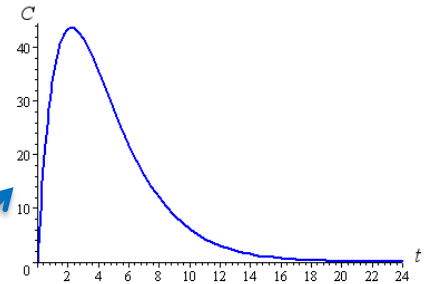
MW, pKa, S_0, LogP

Dissolved API

DISSOLUTION

NUCLEATION/ GROWTH

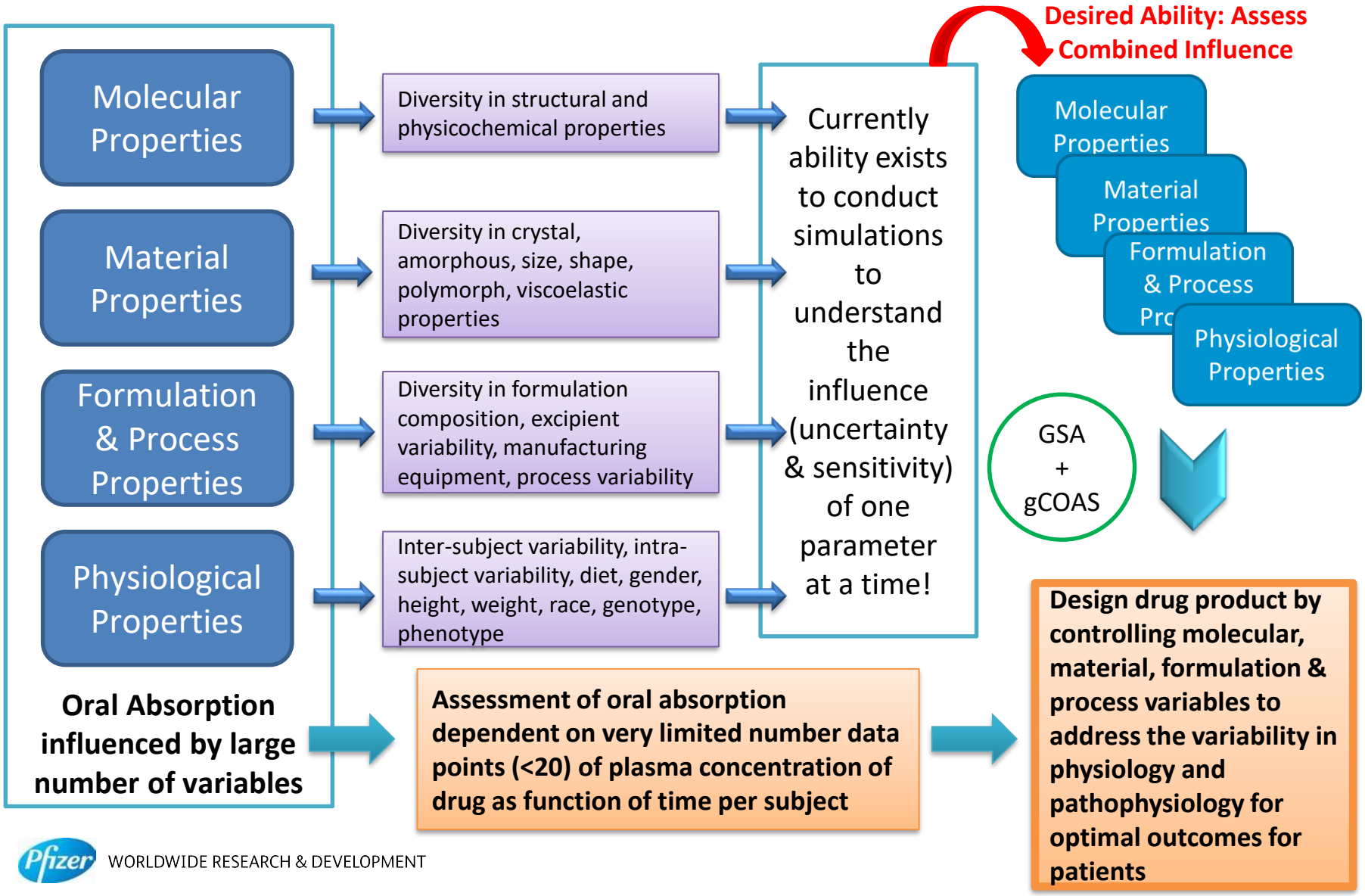
New solid form



Physiological properties

pH, SA, fluid volume, ions

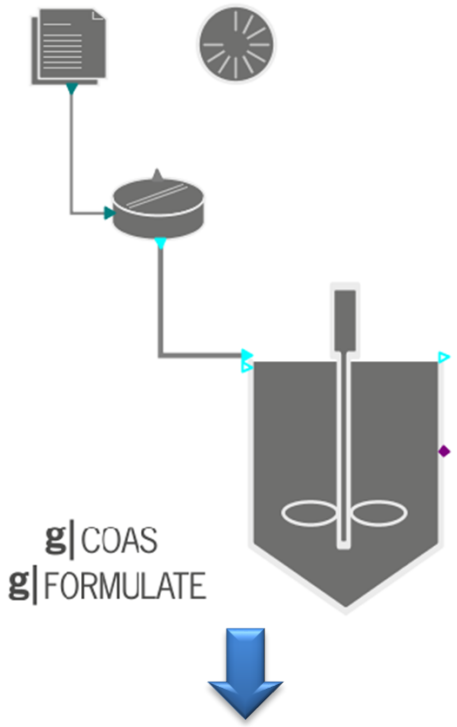
Application of GSA for Oral Absorption: A Vision

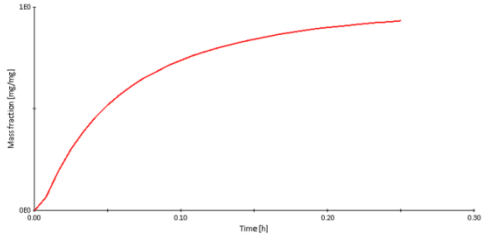


Application of GSA: *In Vitro*

- Variability observed with *in vitro* data could come from different sources:
  - Product
  - Experimental conditions
- GSA has the potential to be used to identify likely source(s) of variability
  - Control sensitive parameters
  - Aid method development

In Vitro Case Study

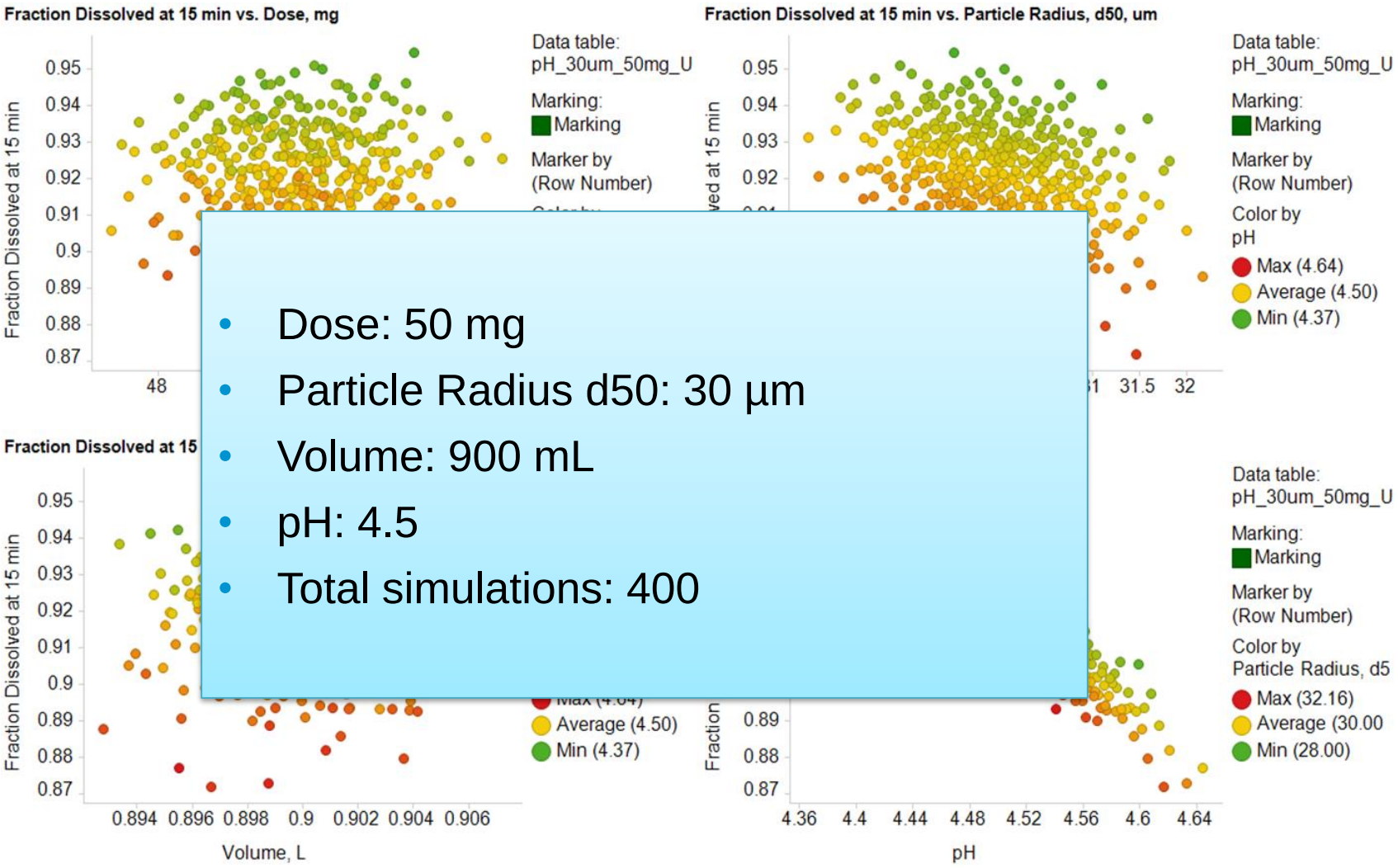




- Model compound
  - Weak base
  - pKa 5
  - S_0 0.07 mg/ml
- Uncertainty analysis conducted to understand impact of variability around product/experimental parameters on fraction dissolved
  - Input (variables): dose, particle size, volume of dissolution media, pH
  - Output (response): fraction dissolved at 15 min

Uncertainty Analysis:

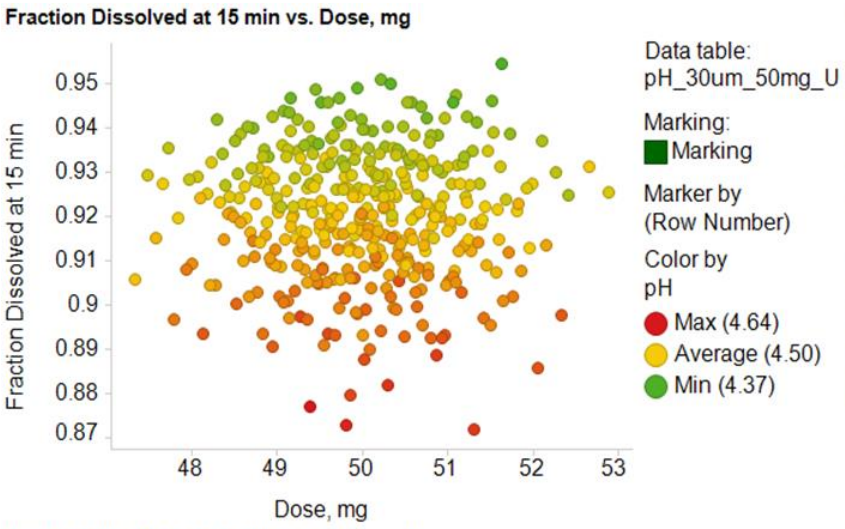
Influence of experimental parameters on fraction dissolved

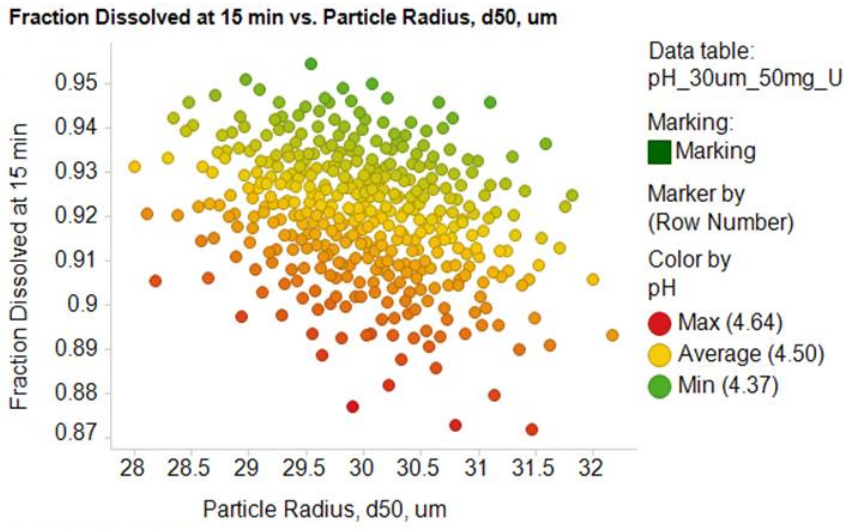


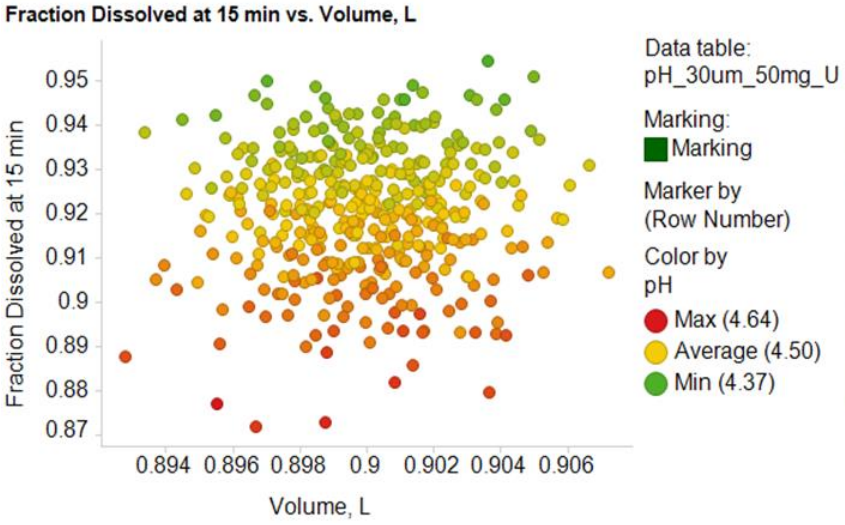
- Dose: 50 mg
- Particle Radius d50: 30 µm
- Volume: 900 mL
- pH: 4.5
- Total simulations: 400

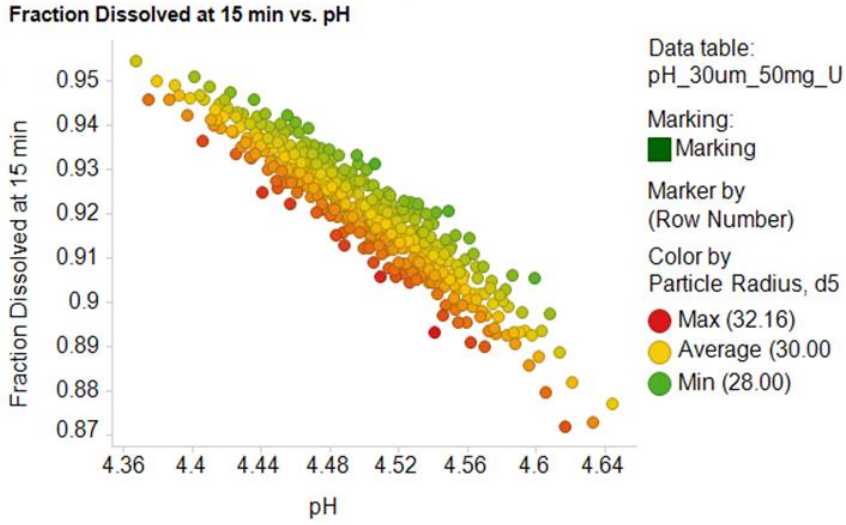
Uncertainty Analysis:

Influence of experimental parameters on fraction dissolved

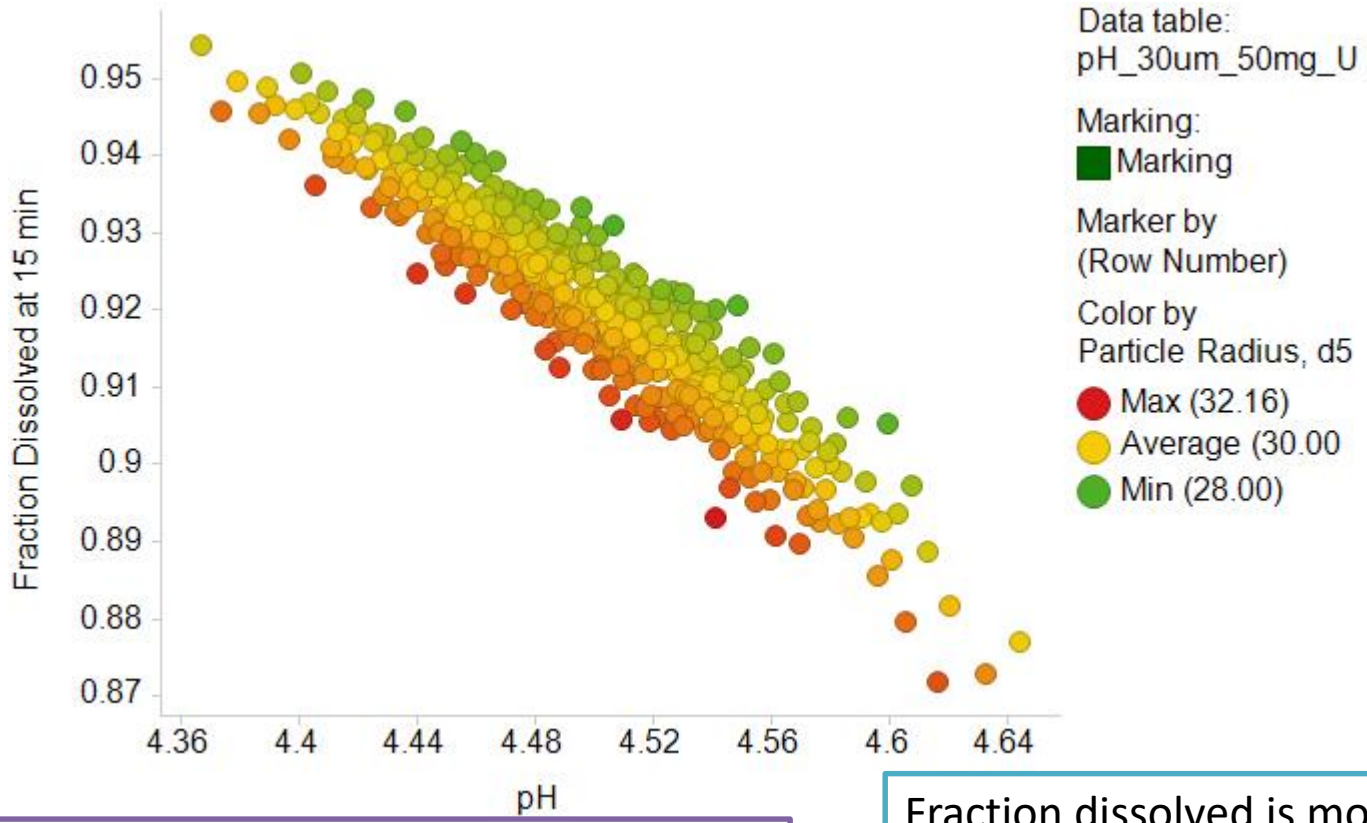








Influence of pH on Fraction Dissolved



Estimated total time to execute GSA: 0.52 hrs
Estimated total time to execute individual simulations: 8.6 hours

Fraction dissolved is most sensitive to pH vs. other parameters tested. Data also shows also a trend in average particle size – at a given pH, the smaller particles have a higher fraction dissolved than the larger particles

Sensitivity Analysis:
Virtual DoE for development of dissolution test method

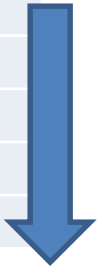
- 30,000 Realizations:

Results of sensitivity analysis show strong dependence on pH of media and a slight dependence on the average particle radius, confirming visual trends presented.

Factor	Total Effect Index
Volume	7.03E-07
Dose	0.001386
pH	0.832935
d50	0.169915
Sum	1.004

Simultaneous evaluation of Influence of dose, particle size , pH, volume of media on % drug dissolved

# Realizations	Sum of Total Effect Indicies
300	1.421
6000	1.016
18000	1.006
30000	1.004
60000	1.003



As the number of simulations is increased, the sum of the total effect indices converge to 1. The trend in factor sensitivity did not change in this case with a small number of samples, but the confidence in the sensitivity increased with the number of samples.

Conducting GSA simulations must be based on achieving balance between computational time versus confidence in identification of most sensitive parameters

Application of GSA: *In Vivo*

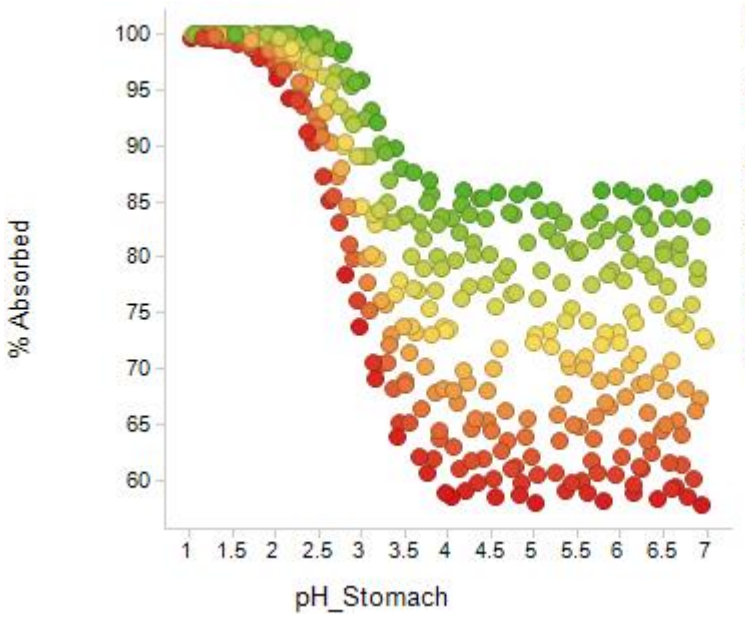
- Physiology settings in oral absorption models typically based on 'textbook' healthy humans
  - Possibly representative of healthy volunteers in early clinical studies
  - Patient population may have different physiological parameters depending on age, disease state, medication etc.
    - Gastric pH
    - Transit time
    - Permeability
- GSA can be used in combination with gCOAS to understand bioperformance of drug in different populations

In Vivo Case Study 1: Weakly Basic Compound

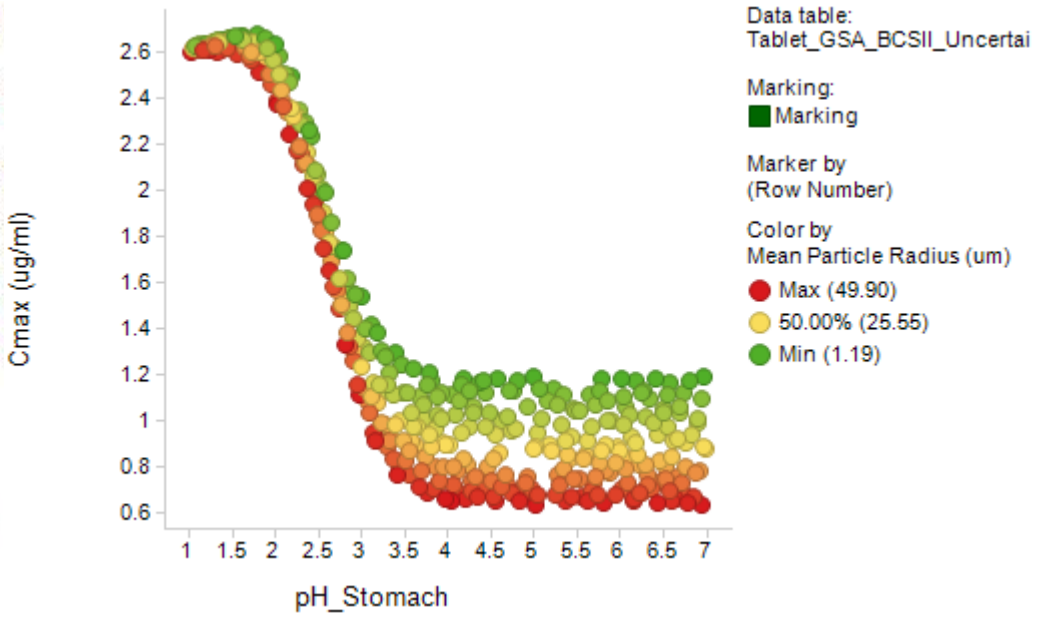
Impact of drug & physiological parameters on oral absorption

- Model BCS II weak base
  - pKa 4.5
  - Log P 2
  - S_0 0.005 mg/ml
  - P_{app} 25×10^{-6} cm/sec
- Uncertainty analysis conducted to understand the impact of different parameters on the bioperformance of the tablet
  - Variables:
    - Particle size
    - Gastric pH

GSA Results:
Influence of Particle Size and Gastric pH



% absorbed



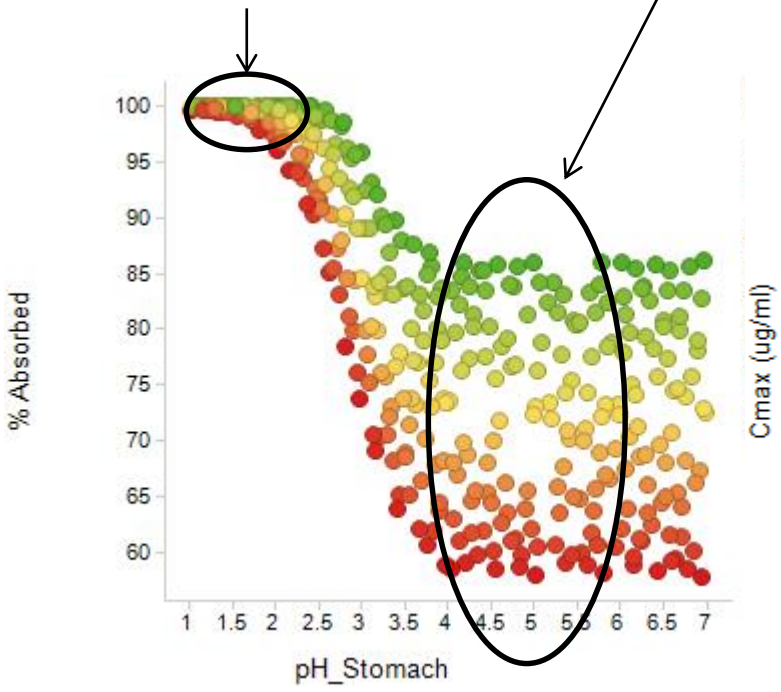
C_{max}

Estimated total time to execute GSA: 17-20 hrs
Estimated total time to execute individual simulations: 4.5 days

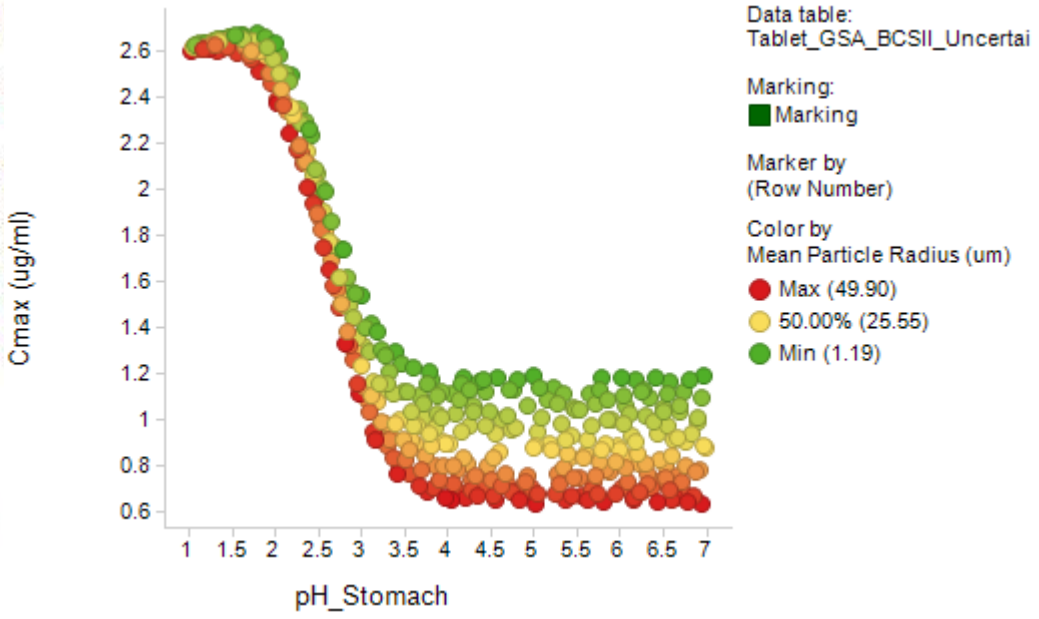
GSA Results:
Influence of Particle Size and Gastric pH

Formulation performance in healthy volunteers

Formulation performance in patient population



% absorbed

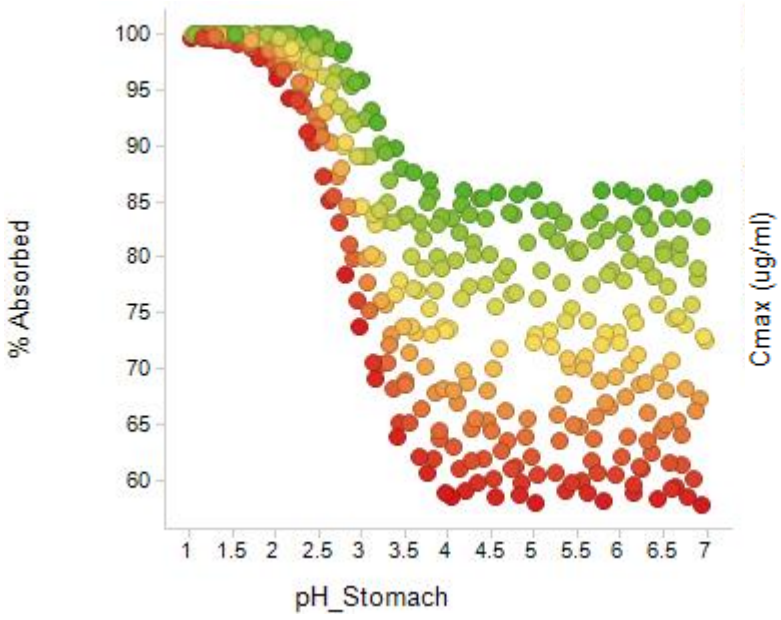


C_{max}

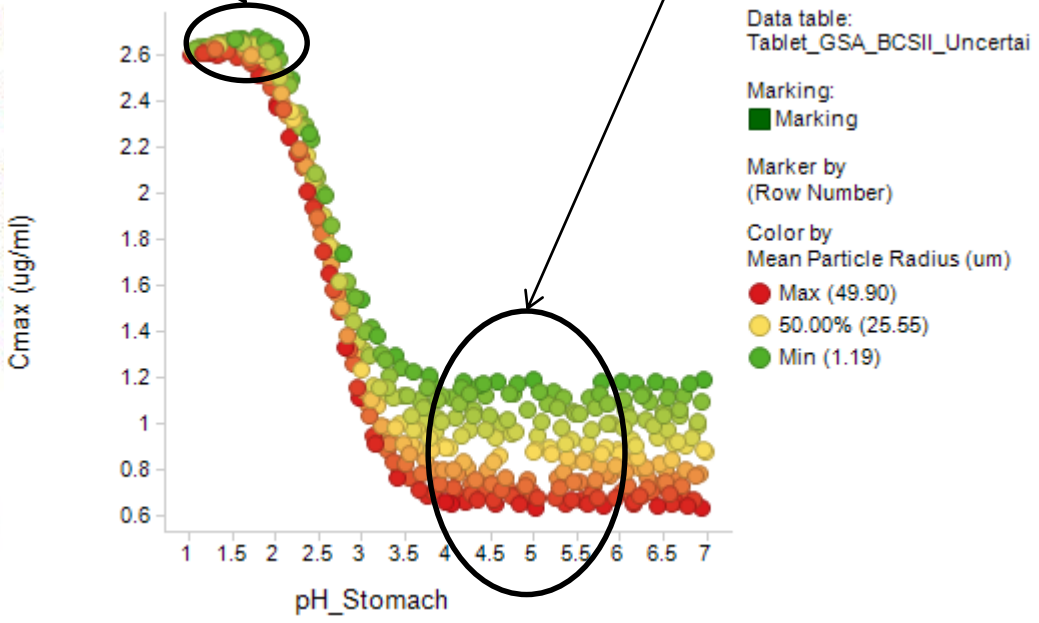
GSA Results:
Influence of Particle Size and Gastric pH

Formulation performance in healthy volunteers

Formulation performance in patient population



% absorbed

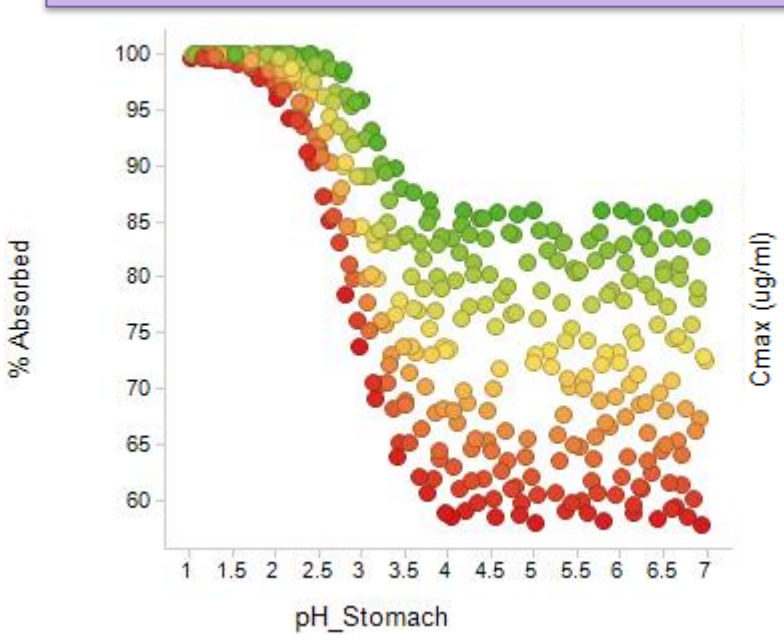


C_{max}

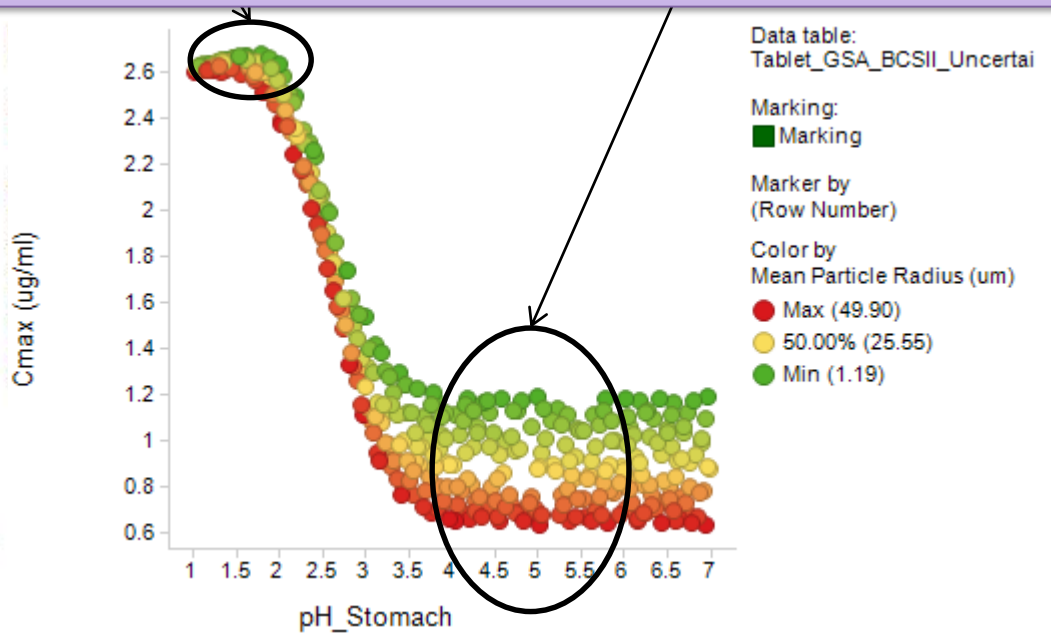
GSA Results:
Influence of Particle Size and Gastric pH

API particle size has no impact on tablet performance in healthy volunteers but significant impact on % absorbed in patient population

Use of GSA highlights the need for setting particle size specifications to ensure right exposure / profile obtained in the patient population



% absorbed



C_{max}

In Vivo Case Study 2: Neutral compound

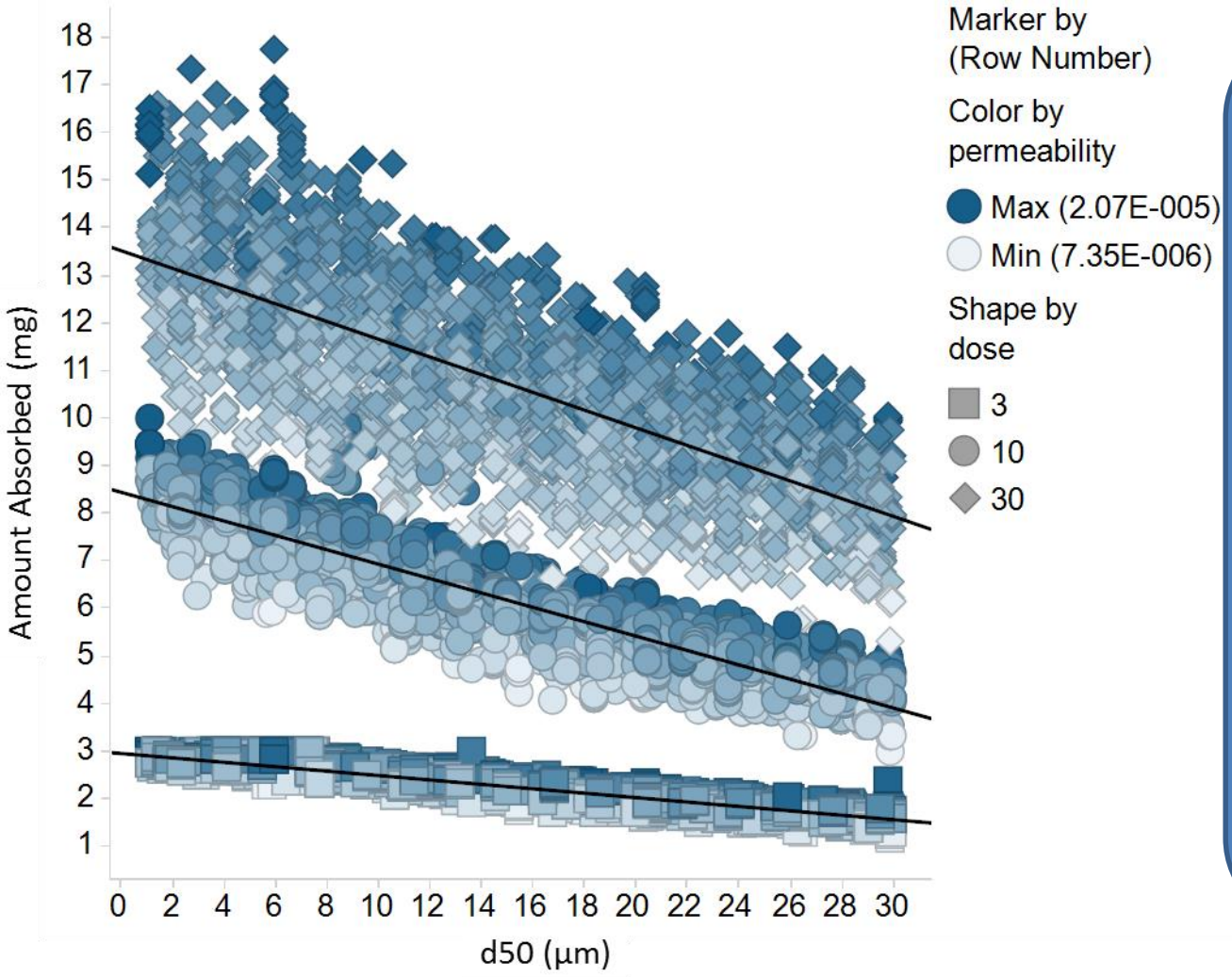
Impact of drug & physiological parameters on absorption

- Neutral compound
  - S_0 0.010 mg/ml

- Uncertainty analysis conducted using the following variables
  - Dose: 3, 10, 30 mg
    - Expect amount absorbed increase with increasing dose
  - Particle size: 1 – 30 µm (d50)
    - Expect amount absorbed decrease with increasing particle size
  - Permeability: P_{app} = 11.5 – 16.5 ($x10^{-6}$ cm/sec)
    - Expect amount absorbed to increase with increasing permeability
  - Physiology:
    - Residence time in stomach: 10 -120 min
    - Residual volume in each intestinal compartment: ± 20% nominal

GSA Results: One Perspective

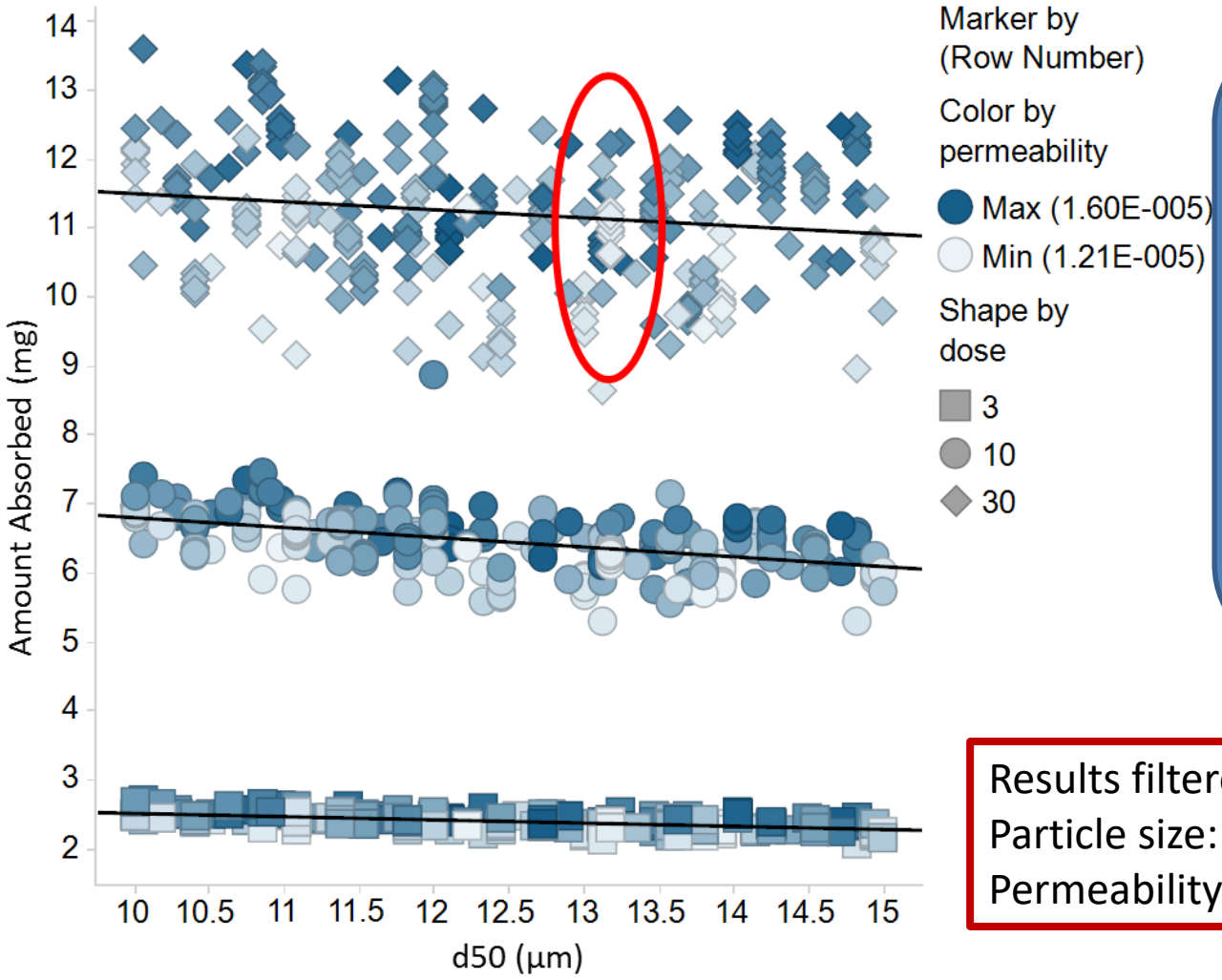
Impact of Drug & Permeability Parameters on Amount Absorbed



Based on input properties, trends expected are generally observed:

- Amount absorbed increases with increase in dose
- Amount absorbed decreases with increase in particle size
- Amount absorbed increases with increase in permeability

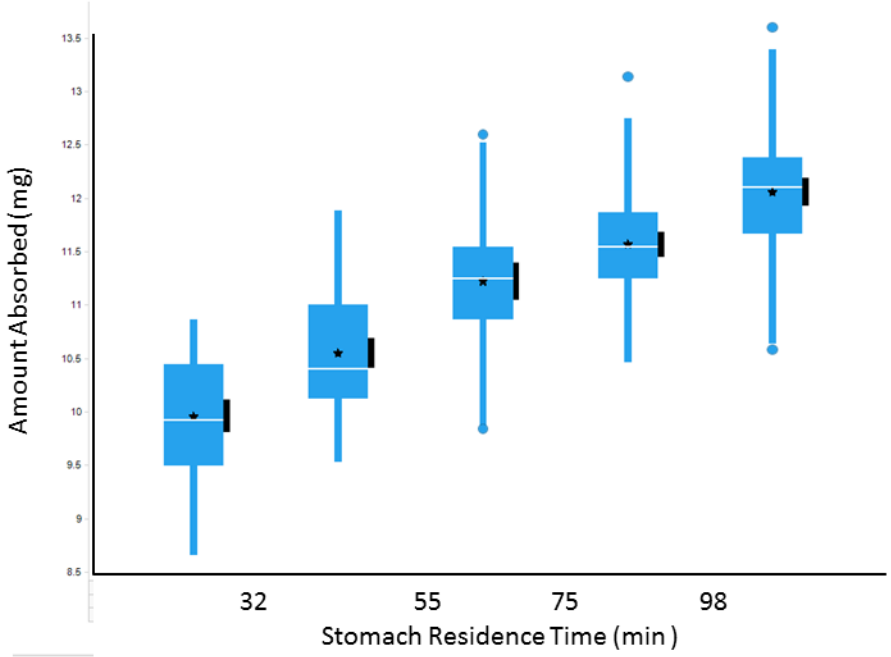
Closer Inspection of GSA Results



Still see the overall trend for dose and particle size, but more variability and outliers with permeability including cases where the permeability trend "flips."

Results filtered to :
Particle size: 10 - 15 µm
Permeability: 13.8 – 14.2 ($x10^{-6}$) cm/sec

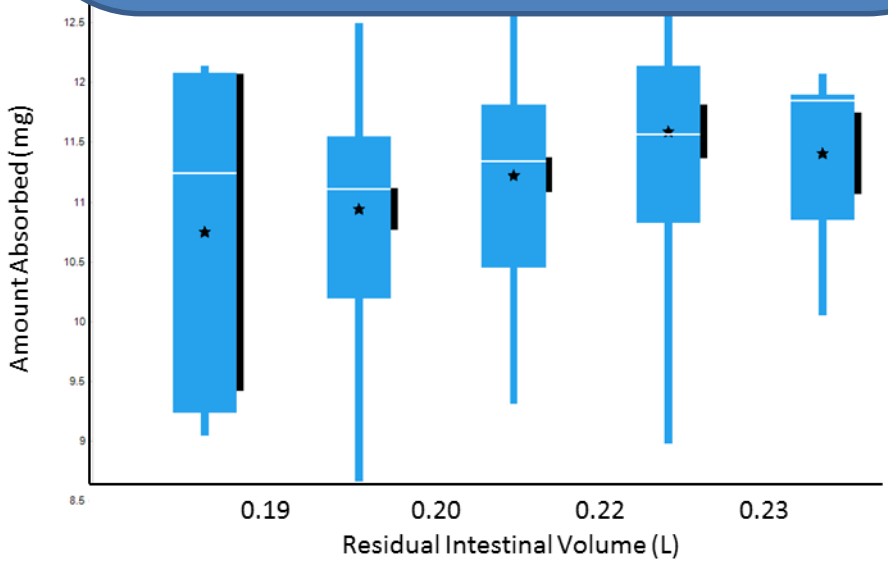
Assessment of Impact of Physiological Parameters on Absorption



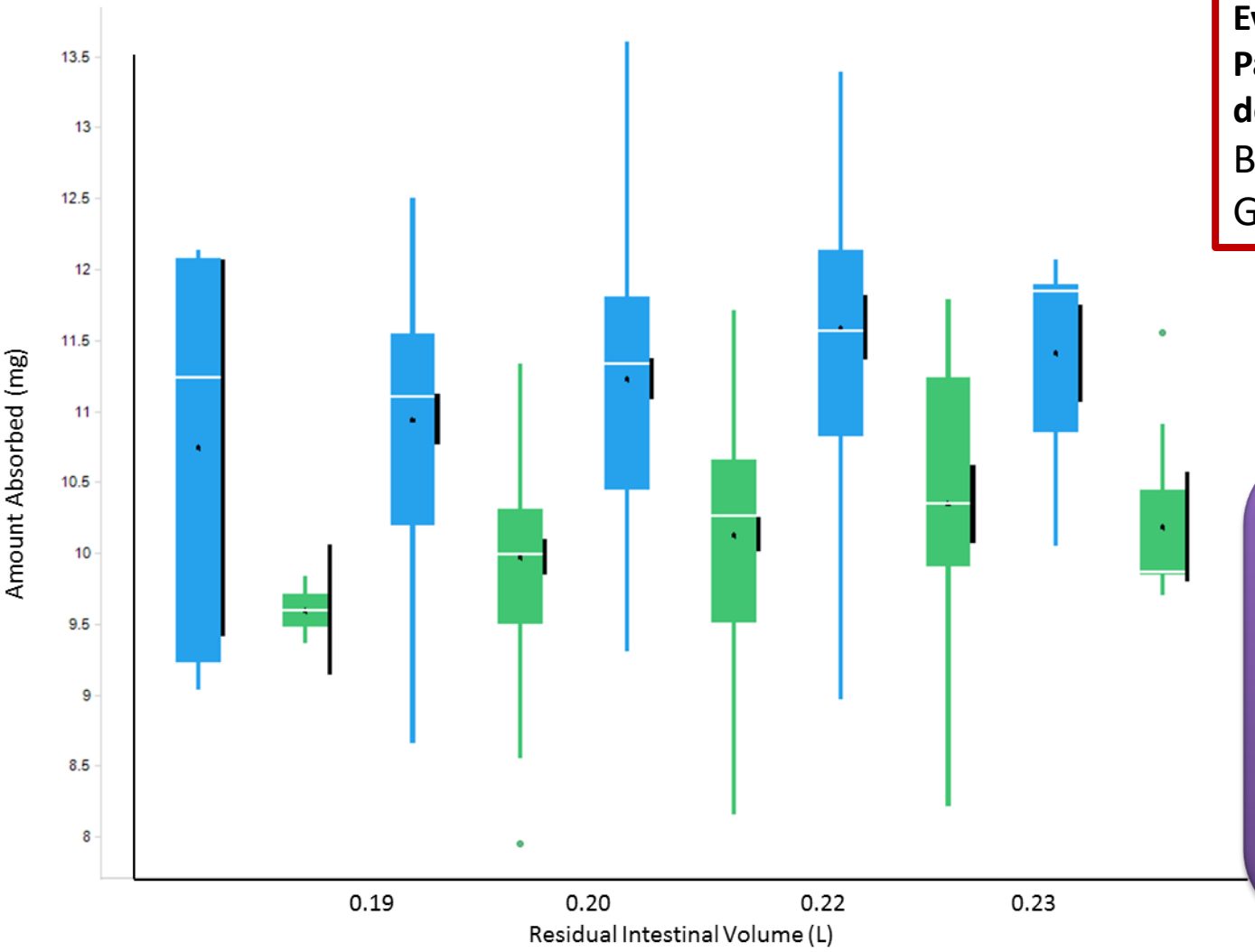
30 mg Dose: Stomach residence time showed a positive trend on total mass absorbed (impact of dissolution). Intestinal Residual Volume was not a sensitive parameter; no clear trend was observed.

Combination of all 3 physiological parameters (gastric retention, residual intestinal volume and permeability) contributes to overall variability in absorption.

Varying physiological parameters in GSA provided a methodology to simulate inter-subject variability including outliers in gCOAS model



Potential Application of GSA in Clinical Study Design



Evaluation of Uncertainty in Particle Size (d50) for 30 mg dose

Blue = 10-15 µm

Green = 15-20 µm

Simulations provide insight on degree of control of particle size needed to achieve BE in light of variability in physiological parameters

Conclusions

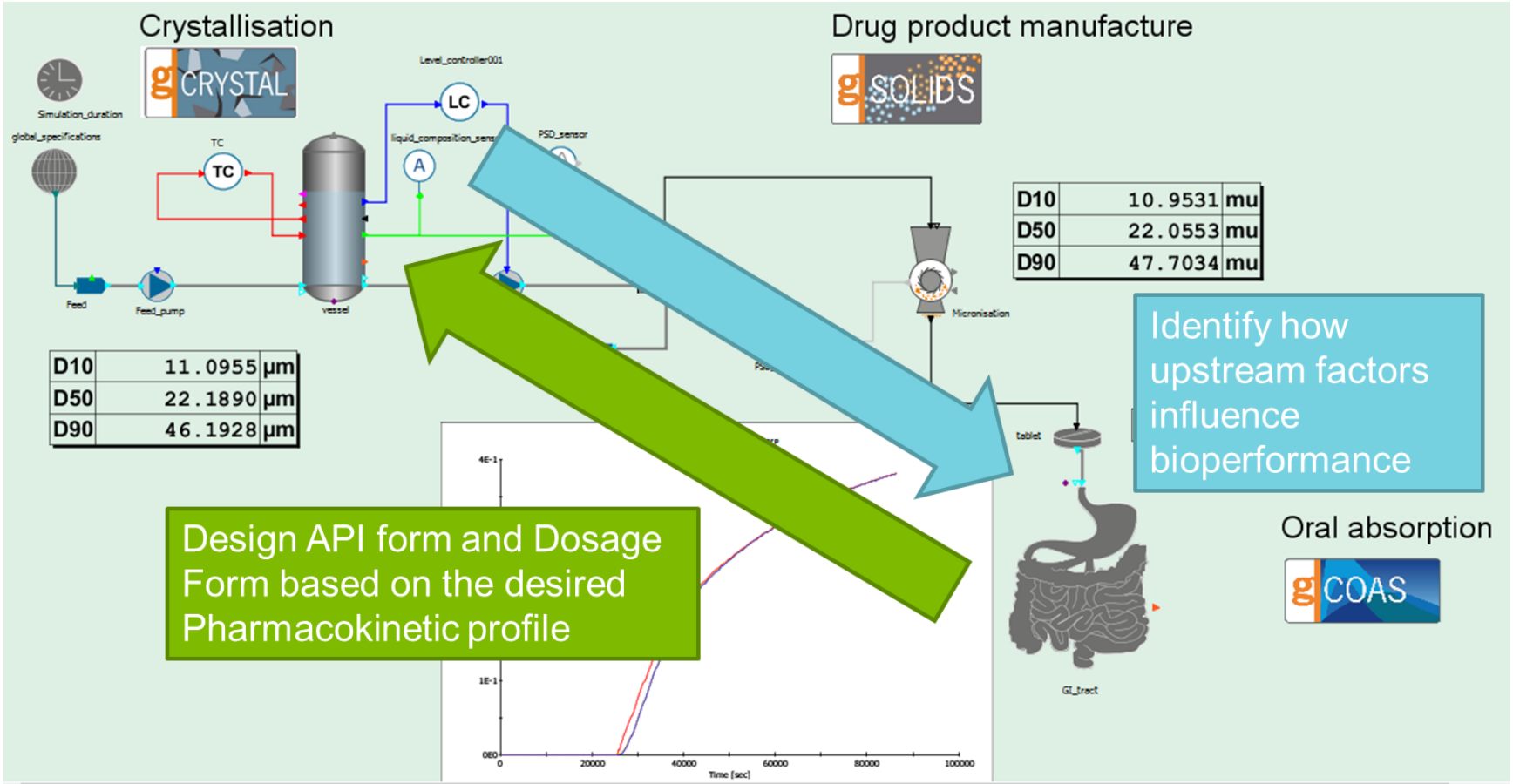
- GSA emerging as an invaluable new tool for gCOAS
  - Can be used with both *in vitro* and *in vivo* gCOAS modules
  - Ability to evaluate impact of combining molecular, material and physiological properties on oral absorption
  - Computational capacity must be balanced with model complexity

- Key advantages of GSA
  - Efficiently conducts uncertainty and sensitivity analysis on a diverse range of parameters
  - Enables prospective predictions of potential outcomes i.e. identify biopharmaceutics risks for development of drug

- GSA can bring significant added value (reduction in cost and time) to simulations by enabling identification of risks and thus provide development of risk mitigation strategies in clinical studies or making key decisions regarding selection of molecules and design of superior drug products

Conclusions

Desired outcome can be achieved for the patient with minimal iterative clinical studies to address bioavailability & bioequivalence



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  Sean Bermingham, Edd Close